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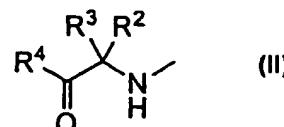
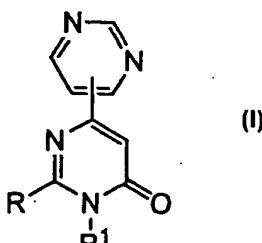
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(54) Title: 3-SUBSTITUTED-4-PYRIMIDONE DERIVATIVES

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(III)

may be substituted, a naphthalene ring which may be substituted, an indan ring which may be substituted, or an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom and nitrogen atom, and having 5 to 10 ring-constituting atoms in total.

(57) Abstract: A pyrimidone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof having inhibitory activity against tau protein kinase 1: wherein R₁ represents a C₁-C₁₂ alkyl group which may be substituted; R represents, for example, a group represented by the following formula (II): wherein R₂ and R₃ independently represent a hydrogen atom or a C₁-C₈ alkyl group; R⁴ represents a benzene ring which

DESCRIPTION

3-SUBSTITUTED-4-PYRIMIDONE DERIVATIVES

Technical Field

The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases mainly caused by abnormal activity of tau protein kinase 1, such as neurodegenerative diseases (e.g. Alzheimer disease).

Background Art

Alzheimer disease is progressive senile dementia, in which marked cerebral cortical atrophy is observed due to degeneration of nerve cells and decrease of nerve cell number. Pathologically, numerous senile plaques and neurofibrillary tangles are observed in brain. The number of patients has been increased with the increment of aged population, and the disease arises a serious social problem. Although various theories have been proposed, a cause of the disease has not yet been elucidated. Early resolution of the cause has been desired.

It has been known that the degree of appearance of two characteristic pathological changes of Alzheimer disease well correlates to the degree of intellectual dysfunction. Therefore, researches have been conducted from early 1980's to reveal the cause of the disease through molecular level investigations of components of the two pathological changes. Senile plaques accumulate extracellularly, and β amyloid protein has been elucidated as their main component (abbreviated as "A β " hereinafter in the specification: Biochem. Biophys. Res. Commun., 120, 855 (1984); EMBO J., 4, 2757 (1985); Proc. Natl. Acad. Sci. USA, 82, 4245 (1985)). In the other pathological change, i.e., the neurofibrillary tangles, a double-helical filamentous

substance called paired helical filament (abbreviated as "PHF" hereinafter in the specification) accumulate intracellularly, and tau protein, which is a kind of microtubule-associated protein specific for brain, has been revealed as its main component (Proc. Natl. Acad. Sci. USA, 85, 4506 (1988); Neuron, 1, 827 (1988)).

Furthermore, on the basis of genetic investigations, presenilins 1 and 2 were found as causative genes of familial Alzheimer disease (Nature, 375, 754 (1995); Science, 269, 973 (1995); Nature, 376, 775 (1995)), and it has been revealed that presence of mutants of presenilins 1 and 2 promotes the secretion of A β (Neuron, 17, 1005 (1996); Proc. Natl. Acad. Sci. USA, 94, 2025 (1997)). From these results, it is considered that, in Alzheimer disease, A β abnormally accumulates and agglomerates due to a certain reason, which engages with the formation of PHF to cause death of nerve cells. It is also expected that extracellular outflow of glutamic acid and activation of glutamate receptor responding to the outflow may possibly be important factors in an early process of the nerve cell death caused by ischemic cerebrovascular accidents (Sai-shin Igaku [Latest Medicine], 49, 1506 (1994)).

It has been reported that kainic acid treatment that stimulates the AMPA receptor, one of glutamate receptor, increases mRNA of the amyloid precursor protein (abbreviated as "APP" hereinafter in the specification) as a precursor of A β (Society for Neuroscience Abstracts, 17, 1445 (1991)), and also promotes metabolism of APP (The Journal of Neuroscience, 10, 2400 (1990)). Therefore, it has been strongly suggested that the accumulation of A β is involved in cellular death due to ischemic cerebrovascular disorders. Other diseases in which abnormal accumulation and agglomeration of A β are observed include, for example, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, Lewy body disease (Shin-kei Shinpo [Nerve Advance], 34, 343 (1990); Tanpaku-shitu Kaku-san Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)) and the like. Furthermore, as diseases showing neurofibrillary tangles due to the PHF accumulation, examples include

progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease and the like (Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 36, 2 (1991); Igaku no Ayumi [Progress of Medicine], 158, 511 (1991); Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)).

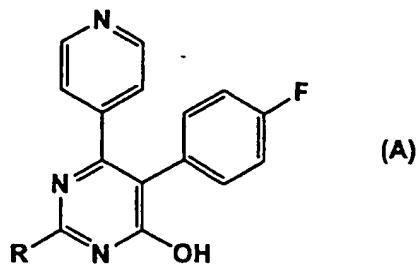
The tau protein is generally composed of a group of related proteins that forms several bands at molecular weights of 48-65 kDa in SDS-polyacrylamide gel electrophoresis, and it promotes the formation of microtubules. It has been verified that tau protein incorporated in the PHF in the brain suffering from Alzheimer disease is abnormally phosphorylated compared with usual tau protein (J. Biochem., 99, 1807 (1986); Proc. Natl. Acad. Sci. USA, 83, 4913 (1986)). An enzyme catalyzing the abnormal phosphorylation has been isolated. The protein was named as tau protein kinase 1 (abbreviated as "TPK1" hereinafter in the specification), and its physicochemical properties have been elucidated (Seikagaku [Biochemistry], 64, 308 (1992); J. Biol. Chem., 267, 10897 (1992)). Moreover, cDNA of rat TPK1 was cloned from a rat cerebral cortex cDNA library based on a partial amino acid sequence of TPK1, and its nucleotide sequence was determined and an amino acid sequence was deduced (Japanese Patent Un-examined Publication [Kokai] No. 6-239893/1994). As a result, it has been revealed that the primary structure of the rat TPK1 corresponds to that of the enzyme known as rat GSK-3 β (glycogen synthase kinase 3 β , FEBS Lett., 325, 167 (1993)).

It has been reported that A β , the main component of senile plaques, is neurotoxic (Science, 250, 279 (1990)). However, various theories have been proposed as for the reason why A β causes the cell death, and any authentic theory has not yet been established. Takashima et al. observed that the cell death was caused by A β treatment of fetal rat hippocampus primary culture system, and then found that the

TPK1 activity was increased by $\text{A} \beta$ treatment and the cell death by $\text{A} \beta$ was inhibited by antisense of TPK1 (Proc. Natl. Acad. Sci. USA, 90, 7789 (1993); Japanese Patent Un-examined Publication [Kokai] No. 6-329551/1994).

In view of the foregoing, compounds which inhibit the TPK1 activity may possibly suppress the neurotoxicity of $\text{A} \beta$ and the formation of PHF and inhibit the nerve cell death in the Alzheimer disease, thereby cease or defer the progress of the disease. The compounds may also be possibly used as a medicament for therapeutic treatment of ischemic cerebrovascular disorder, Down syndrome, cerebral amyloid angiopathy, cerebral bleeding due to Lewy body disease and the like by suppressing the cytotoxicity of $\text{A} \beta$. Furthermore, the compounds may possibly be used as a medicament for therapeutic treatment of neurodegenerative diseases such as progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration, frontotemporal dementia, vascular dementia, traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma, as well as other diseases such as non-insulin dependent diabetes, obesity, manic depressive illness, schizophrenia, alopecia, breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia, and several virus-induced tumors.

As structurally similar compounds to the compounds of the present invention represented by formula (I) described later, compounds represented by the following formula (A) are known:



wherein R represents 2,6-dichlorobenzyl group, 2-(2-chlorophenyl)ethylamino group, 3-phenylpropylamino group, or 1-methyl-3-phenylpropylamino group (WO98/24782). The compounds represented by formula (A) are characterized to have 4-fluorophenyl group at the 5-position of the pyrimidine ring and a hydroxy group at the 4-position, and not falling within the scope of the present invention. Moreover, main pharmacological activity of the compounds represented by formula (A) is anti-inflammatory effect, whereas the compounds of the present invention represented by formula (I) are useful as a TPK1 inhibitor or a medicament for therapeutic treatment of neutodegenerative diseases, and therefore, their pharmacological activities are totally different to each other.

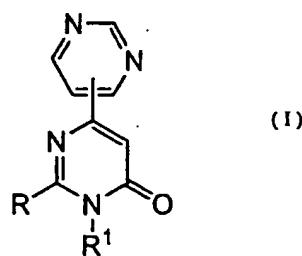
Object to be Achieved by the Invention

An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases such as Alzheimer disease. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables radical prevention and/or treatment of the neutodegenerative diseases such as Alzheimer disease by inhibiting the TPK1 activity to suppress the neurotoxicity of $\text{A}\beta$ and the formation of the PHF and by inhibiting the death of nerve cells.

Means to Achieve the Object

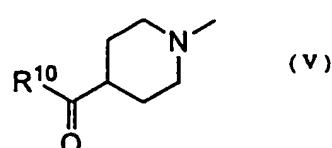
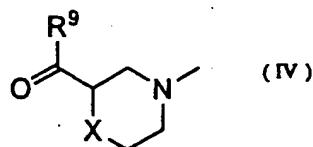
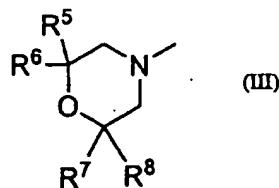
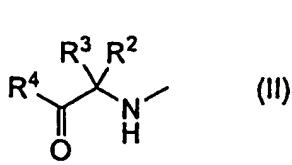
In order to achieve the foregoing object, the inventors of the present invention conducted screenings of various compounds having inhibitory activity against the phosphorylation of TPK1. As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases. The present invention was achieved on the basis of these findings.

The present invention thus provide a pyrimidone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:



wherein R¹ represents a C₁-C₁₂ alkyl group which may be substituted;

R represents any one of groups represented by the following formulas (II) to (V):



wherein R² and R³ independently represent a hydrogen atom or a C₁-C₈ alkyl group; R⁴ represents a benzene ring which may be substituted, a naphthalene ring which may be substituted, an indan ring which may be substituted, a tetrahydronaphthalene ring which may be substituted, or an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom and nitrogen atom, and having 5 to 10 ring-constituting atoms in total;

R⁵ represents a C₁-C₈ alkyl group which may be substituted, a C₃-C₈ cycloalkyl group which may be substituted, a benzene ring which may be substituted, a naphthalene ring which may be substituted, an indan ring which may be substituted, a tetrahydronaphthalene ring which may be substituted, or an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms in total;

R⁶ represents a hydrogen atom, a C₁-C₈ alkyl group which may be substituted, a benzene ring which may be substituted;

or R⁵ and R⁶ may bind to each other to form together with the carbon to which R⁵ and R⁶ are attached an optionally substituted spiro carbocyclic ring having 3 to 11 ring-constituting atoms in total;

R⁷ and R⁸ independently represent a hydrogen atom or a C₁-C₈ alkyl group, or R⁷ and R⁸ may combine to each other to form a C₂-C₆ alkylene group;

R⁹ and R¹⁰ represent a C₁-C₈ alkyl group which may be substituted, a C₃-C₈ cycloalkyl group which may be substituted, a benzene ring which may be substituted, a naphthalene ring which may be substituted, an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms in total, or R⁹ and R¹⁰ represent -N(R¹¹)(R¹²) wherein R¹¹ represents a hydrogen atom, a C₁-C₈

alkyl group; and R¹² represents a C₁-C₈ alkyl group, a benzene ring which may be substituted, a naphthalene ring which may be substituted, or an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms in total;
and X represents CH₂, O or NR¹³ wherein R¹³ represents a hydrogen atom or a C₁-C₈ alkyl group.

According to preferred embodiments of the present invention, provided are:
the aforementioned pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof, wherein R¹ is methyl group;
the aforementioned pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof, wherein R is the group represented by formula (II);
the aforementioned pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof, wherein each of R² and R³ is hydrogen atom;
the aforementioned pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof, wherein R is the group represented by formula (III);
the aforementioned pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof, wherein R⁶ is hydrogen atom;
the aforementioned pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof, wherein each of R⁷ and R⁸ is hydrogen atom;
the aforementioned pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof, wherein each of R⁷ and R⁸ is methyl group;
the aforementioned pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof, wherein R is the group represented by formula (IV);
the aforementioned pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof, wherein R⁹ is a benzene ring which may be substituted;

the aforementioned pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof, wherein X is CH_2 ;

the aforementioned pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof, wherein X is O;

the aforementioned pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof, wherein R is the group represented by formula (V);

the aforementioned pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof, wherein R^{10} is a benzene ring which may be substituted; and

the aforementioned pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof, wherein R^{10} is a heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5 to 10 which may be substituted.

From another aspect, the present invention provides a medicament comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivative represented by the aforementioned formula (I) and a salt thereof, and a solvate thereof and a hydrate thereof, and a tau protein kinase 1 inhibitor selected from the group consisting of the pyrimidone derivative represented by the aforementioned formula (I) and a salt thereof, and a solvate thereof and a hydrate thereof.

According to preferred embodiments of the aforementioned medicament, provided are the aforementioned medicament which is used for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity;

the aforementioned medicament which is used for preventive and/or therapeutic treatment of a neurodegenerative disease;

the aforementioned medicament, wherein the disease is selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down

syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration, frontotemporal dementia, vascular dementia, traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma; and

the aforementioned medicament, wherein the disease is selected from the group consisting of non-insulin dependent diabetes, obesity, manic depressive illness, schizophrenia, alopecia, breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia, and a virus-induced tumor.

According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivative of formula (I) and the physiologically acceptable salt thereof, and the solvate thereof and the hydrate thereof; and a use of a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivative of formula (I) and the physiologically acceptable salt thereof, and the solvate thereof and the hydrate thereof for the manufacture of the aforementioned medicament.

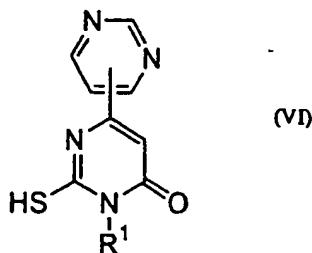
From further aspect of the present invention, provided are a pyrimidone derivative represented by formula (VI) or a salt thereof, or a solvate thereof or a hydrate thereof:

syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration, frontotemporal dementia, vascular dementia, traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma; and

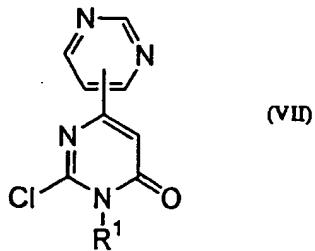
the aforementioned medicament, wherein the disease is selected from the group consisting of non-insulin dependent diabetes, obesity, manic depressive illness, schizophrenia, alopecia, breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia, and a virus-induced tumor.

According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivative of formula (I) and the physiologically acceptable salt thereof, and the solvate thereof and the hydrate thereof; and a use of a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivative of formula (I) and the physiologically acceptable salt thereof, and the solvate thereof and the hydrate thereof for the manufacture of the aforementioned medicament.

From further aspect of the present invention, provided are a pyrimidone derivative represented by formula (VI) or a salt thereof, or a solvate thereof or a hydrate thereof:



wherein R¹ represents a C₁-C₁₂ alkyl group which may be substituted, and a pyrimidone derivative represented by formula (VII) or a salt thereof, or a solvate thereof or a hydrate thereof:



wherein R¹ represents a C₁-C₁₂ alkyl group which may be substituted.

Best Mode for Carrying Out the Invention

The alkyl group used herein may be either linear or branched. The C₁-C₁₂ alkyl group represented by R¹ may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, or a linear or branched heptyl group, octyl group, nonyl group, decyl group, undecyl group or dodecyl group. In the specification, when a functional group is defined as "which may be substituted" or "optionally substituted", the number of substituents as well as their types and substituting positions are not particularly limited, and when two or more substituents are present, they may be the same or different.

When the C₁-C₁₂ alkyl group represented by R¹ has one or more substituents,

the alkyl group may have one or more substituents selected from the group consisting of a C₁-C₆ alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group; amino group, C₁-C₃ alkylamino group or C₂-C₆ dialkylamino group; a C₆-C₁₀ aryl group such as phenyl group, 1-naphthyl group, and 2-naphthyl group;

The C₁-C₈ alkyl group represented by R² or R³ may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, or a linear or branched heptyl group or octyl group.

When the benzene ring, the naphthalene ring, the indan ring, the tetrahydronaphthalene ring, or the heterocyclic ring represented by R⁴ or R⁵ has one or more substituents, the rings may have one or more substituents selected from the groups consisting of a C₁-C₅ alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group; C₃-C₆ cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group; a C₃-C₆ cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group; a C₁-C₅ alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C₄-C₇ cycloalkylalkoxy group such as cyclopropylmethoxy group, cyclopentylmethoxy group; a C₁-C₅ alkylthio group such as methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a C₁-C₅ alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C₁-C₅ halogenated alkyl group such as

trifluoromethyl group; a C₁-C₆ halogenated alkoxy group such as trifluoromethoxy group, 2,2,2-trifluoroethoxy group; hydroxyl group; cyano group; nitro group; formyl group; a C₂-C₆ alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; benzene ring which may be substituted, naphthalene ring which may be substituted, an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom and nitrogen atom, and having 5 to 10 ring-constituting atoms, phenoxy group which may be substituted or phenylamino group which may be substituted; amino group; a C₁-C₅ monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C₂-C₁₀ dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; a C₂-C₁₀ monoalkylaminomethyl group such as methylaminomethyl group, ethylaminomethyl group, propylaminomethyl group, isopropylaminomethyl group, butylaminomethyl group, isobutylaminomethyl group, tert-butylaminomethyl group, pentylaminomethyl group, isopentylaminomethyl group; a C₃-C₁₁ dialkylaminomethyl group such as dimethylaminomethyl group, diethylaminomethyl group, ethylmethylaminomethyl group, methylpropylaminomethyl group; pyrrolidinylmethyl group; piperidinylmethyl group; morpholinomethyl group; piperazinylmethyl group; pyrrolymethyl group; imidazolymethyl group; pyrazolymethyl group; and triazolymethyl group.

When the benzene ring, the naphthalene ring, the indan ring, the tetrahydronaphthalene ring or the heterocyclic ring has one or more substituents, the substituent may further have one or more substituents selected from the group consisting of a C₁-C₅ alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group; C₃-C₆ cycloalkyl

group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group; a C₃-C₆ cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group; a C₁-C₅ alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C₄-C₇ cycloalkylalkoxy group such as cyclopropylmethoxy group, cyclopentylmethoxy group; a C₁-C₅ alkylthio group such as methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a C₁-C₅ alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C₁-C₅ halogenated alkyl group such as trifluoromethyl group; a C₁-C₅ halogenated alkoxy group such as trifluoromethoxy group, 2,2,2-trifluoroethoxy group; hydroxyl group; cyano group; nitro group; formyl group; a C₂-C₆ alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; amino group; a C₁-C₅ monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C₂-C₁₀ dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; a C₂-C₁₀ monoalkylaminomethyl group such as methylaminomethyl group, ethylaminomethyl group, propylaminomethyl group, isopropylaminomethyl group, butylaminomethyl group, isobutylaminomethyl group, tert-butylaminomethyl group, pentylaminomethyl group, isopentylaminomethyl group; a C₃-C₁₁ dialkylaminomethyl group such as dimethylaminomethyl group, diethylaminomethyl group, ethylmethylaminomethyl group, methylpropylaminomethyl group and the like.

The heterocyclic ring having 1 to 4 hetero atoms selected from the group

consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms represented by R⁴ or R⁵ may be, for example, furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, dihydrobenzofuran, isobenzofuran ring, benzodioxole ring, chromene ring, chroman ring, isochroman ring, thiophene ring, benzothiophene ring, pyrrole ring, pyrrolidine ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, benzotriazole ring, tetrahydroisoquinoline ring, benzothiazolinone ring, benzoxazolinone ring, purine ring, quinolizine ring, quinoline ring, phthalazine ring, naphthyridine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, oxadiazole ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, benzodioxole ring, dioxane ring, benzodioxane ring, dithian ring, morpholine ring, thiomorpholine ring, and phthalimide ring.

The C₁-C₈ alkyl group represented by R⁵, R⁶, R⁷ or R⁸ may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, or a linear or branched heptyl group or octyl group.

The C₃-C₈ cycloalkyl group represented by R⁵ may be, for example, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group or cyclooctyl group.

When the C₁-C₈ alkyl group or C₃-C₈ cycloalkyl group represented by R⁵ or the C₁-C₈ alkyl group represented by R⁶ has one or more substituents, the group may

have one or more substituents selected from the groups consisting of a halogen atom, a C₁-C₈ alkoxy group, a C₃-C₈ cycloalkyl group, a benzene ring which may be substituted, a naphthalene ring which may be substituted, phenoxy group which may be substituted or phenylamino group which may be substituted; amino group, a C₁-C₆ alkylamino group, a C₂-C₁₂ dialkylamino group, 1-pyrrolidinyl group, 1-piperidinyl group, 1-morpholinyl group, 1-(tetrahydro-1,2,3,4-quinolinyl) group, or 1-(tetrahydro-1,2,3,4-isoquinolinyl) group.

When the benzene ring represented by R⁶ has one or more substituents, the ring may have one or more substituents selected from the group consisting of a C₁-C₅ alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group; a C₃-C₆ cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group; a C₃-C₆ cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group; a C₁-C₅ alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C₄-C₇ cycloalkylalkoxyl group such as cyclopropylmethoxy group, cyclopentylmethoxy group; a C₁-C₅ alkylthio group such as methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a C₁-C₅ alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C₁-C₅ halogenated alkyl group such as trifluoromethyl group; a C₁-C₅ halogenated alkoxy group such as trifluoromethoxy group, 2,2,2-trifluoroethoxy group; hydroxyl group; cyano group; nitro group; formyl group; a C₂-C₆ alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; a benzene ring which may be substituted, a naphthalene ring which

may be substituted, an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom and nitrogen atom, and having 5 to 10 ring-constituting atoms, phenoxy group which may be substituted or phenylamino group which may be substituted; amino group; a C₁-C₅ monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C₂-C₁₀ dialkylamino group such as dimethylamino group, ethylmethyldimino group, diethylamino group, methylpropylamino group, and diisopropylamino group; a C₂-C₁₀ monoalkylaminomethyl group such as methylaminomethyl group, ethylaminomethyl group, propylaminomethyl group, isopropylaminomethyl group, butylaminomethyl group, isobutylaminomethyl group, tert-butylaminomethyl group, pentylaminomethyl group, isopentylaminomethyl group; a C₃-C₁₁ dialkylaminomethyl group such as dimethylaminomethyl group, diethylaminomethyl group, ethylmethyldimethyl group, methylpropylaminomethyl group; pyrrolidinylmethyl group; pipelidinylmethyl group; morpholinomethyl group; piperazinylmethyl group; pyrrolylmethyl group; imidazolylmethyl group; pyrazolylmethyl group; triazolylmethyl group.

When the benzene ring represented by R⁶ has one or more substituents, the substituent may further have one or more substituents selected from the groups consisting of a C₁-C₅ alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group; C₃-C₆ cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group; a C₃-C₆ cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group; a C₁-C₅ alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C₄-C₇ cycloalkylalkoxy

group such as cyclopropylmethoxy group, cyclopentylmethoxy group; a C₁-C₆ alkylthio group such as methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a C₁-C₆ alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C₁-C₆ halogenated alkyl group such as trifluoromethyl group; a C₁-C₆ halogenated alkoxy group such as trifluoromethoxy group, 2,2,2-trifluoroethoxy group; hydroxyl group; cyano group; nitro group; formyl group; a C₂-C₆ alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; amino group; a C₁-C₆ monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C₂-C₁₀ dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; a C₂-C₁₀ monoalkylaminomethyl group such as methylaminomethyl group, ethylaminomethyl group, propylaminomethyl group, isopropylaminomethyl group, butylaminomethyl group, isobutylaminomethyl group, tert-butylaminomethyl group, pentylaminomethyl group, isopentylaminomethyl group; a C₃-C₁₁ dialkylaminomethyl group such as dimethylaminomethyl group, diethylaminomethyl group, ethylmethylaminomethyl group, methylpropylaminomethyl group.

When R⁵ and R⁶ combine to each other to form a spiro carbocyclic ring, together with the carbon atom to which R⁵ and R⁶ bind, the carbocyclic ring may be, for example, cyclopropyl ring, cyclobutyl ring, cyclopentyl ring, cyclohexyl ring, cycloheptyl ring, tetrahydrobenzocycloheptene ring, tetrahydronaphthalene ring, indane ring, bicyclo[4,2,0]octa-1,3,5-triene ring.

The C₁-C₆ alkyl group represented by R⁹, R¹⁰, R¹¹, R¹² or R¹³ may be, for

example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, or a linear or branched heptyl group or octyl group.

The C₃-C₈ cycloalkyl group represented by R⁹ or R¹⁰ may be, for example, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group or cyclooctyl group.

When the C₁-C₈ alkyl group or C₃-C₈ cycloalkyl group represented by R⁹ or R¹⁰ has one or more substituents, the group may have one or more substituents selected from, for example, the groups consisting of a halogen atom, C₃-C₈ cycloalkyl group, a benzene ring which may be substituted, a naphthalene ring which may be substituted, an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom and nitrogen atom, and having 5 to 10 ring-constituting atoms in total.

When the benzene ring, the naphthalene ring or the heterocyclic ring represented by R⁹ or R¹⁰ has one or more substituents, the ring may have one or more substituents selected from the group consisting of a C₁-C₅ alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group; C₃-C₆ cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group; a C₃-C₆ cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group; a C₁-C₅ alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C₄-C₇ cycloalkylalkoxyl group such as cyclopropylmethoxy group, cyclopentylmethoxy group; a C₁-C₅ alkylthio group such as methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a C₁-C₅

alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C₁-C₅ halogenated alkyl group such as trifluoromethyl group; a C₁-C₅ halogenated alkoxy group such as trifluoromethoxy group, 2,2,2-trifluoroethoxy group; hydroxyl group; cyano group; nitro group; formyl group; a C₂-C₆ alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; a benzene ring which may be substituted, a naphthalene ring which may be substituted, an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom and nitrogen atom, and having 5 to 10 ring-constituting atoms in total; a phenoxy group which may be substituted; a phenylamino group which may be substituted; an amino group; a C₁-C₅ monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C₂-C₁₀ dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; a C₁-C₅ monoalkylaminomethyl group such as methylaminomethyl group, ethylaminomethyl group, propylaminomethyl group, isopropylaminomethyl group, butylaminomethyl group, isobutylaminomethyl group, tert-butylaminomethyl group, pentylaminomethyl group, isopentylaminomethyl group; a C₂-C₁₀ dialkylaminomethyl group such as dimethylaminomethyl group, diethylaminomethyl group, ethylmethylaminomethyl group, methylpropylaminomethyl group; pyrrolidinylmethyl group; piperidinylmethyl group; morpholinomethyl group; piperazinylmethyl group; pyrrolylmethyl group; imidazolylmethyl group; pyrazolylmethyl group; and triazolylmethyl group.

The heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10

ring-constituting atoms in total represented by R⁹ or R¹⁰ may be, for example, furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, dihydrobenzofuran, isobenzofuran ring, benzodioxol ring, chromene ring, chroman ring, isochroman ring, thiophene ring, benzothiophene ring, pyrrole ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, benzotriazole ring, tetrahydroisoquinoline ring, benzothiazolinone ring, benzoxazolinone ring, purine ring, quinolizine ring, quinoline ring, phthalazine ring, naphthyridine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, oxadiazole ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, benzodioxole ring, dioxane ring, benzodioxane ring, dithian ring, morpholine ring, thiomorpholine ring, or phthalimide ring.

When the benzene ring, the naphthalene ring, or the heterocyclic ring represented by R¹² has one or more substituents, the ring may be substituted by one or more substituents selected from the groups consisting of halogen atoms, a C₁-C₅ alkyl group, a C₃-C₆ cycloalkyl group, a C₃-C₆ cycloalkyloxy group, a C₁-C₅ alkoxy group, a C₄-C₇ cycloalkylalkoxy, a C₁-C₅ alkylthio group, a C₁-C₆ alkylsulfonyl group, a C₁-C₅ halogenated alkyl, and a benzene ring.

When the benzene ring, the naphthalene ring or the heterocyclic ring has one or more substituents, the substituent may further have one or more substituents selected from the group consisting of a C₁-C₅ alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl

group; C₃-C₆ cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group; a C₃-C₆ cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group; a C₁-C₆ alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C₄-C₇ cycloalkylalkoxy group such as cyclopropylmethoxy group, cyclopentylmethoxy group; a C₁-C₆ alkylthio group such as methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a C₁-C₆ alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C₁-C₆ halogenated alkyl group such as trifluoromethyl group; a C₁-C₆ halogenated alkoxy group such as trifluoromethoxy group, 2,2,2-trifluoroethoxy group; hydroxyl group; cyano group; nitro group; formyl group; a C₂-C₆ alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; amino group; a C₁-C₆ monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C₂-C₁₀ dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; a C₂-C₁₀ monoalkylaminomethyl group such as methylaminomethyl group, ethylaminomethyl group, propylaminomethyl group, isopropylaminomethyl group, butylaminomethyl group, isobutylaminomethyl group, tert-butylaminomethyl group, pentylaminomethyl group, isopentylaminomethyl group; a C₃-C₁₁ dialkylaminomethyl group such as dimethylaminomethyl group, diethylaminomethyl group, ethylmethylaminomethyl group, methylpropylaminomethyl group and the like.

R¹ may preferably be a C₁-C₃ alkyl group, more preferably a methyl group.

R² may preferably be a hydrogen atom.

R³ may preferably be a hydrogen atom.

R⁴ may preferably be a benzene ring which may be substituted.

R⁵ may preferably be a benzene ring or a naphthalene ring which may be substituted.

R⁶ may preferably be a hydrogen atom.

R⁷ and R⁸ may preferably be a hydrogen atom or a C₁-C₃ alkyl group.

R⁹ or R¹⁰ may preferably be a benzene ring which may be substituted.

R¹⁰ may preferably be a heterocyclic ring having 1-4 hetero atoms selected oxygen atom, sulfur atom and nitrogen atom, and having total ring-constituting atoms of 5-10 which may be substituted. Particularly preferred R¹⁰ is a benzene ring which may be substituted, a 2,3-dihydroindole ring which may be substituted, or 3,4-dihydro-2H-quinoline ring which may be substituted.

Particularly preferred X is CH₂ or O.

The compounds represented by the aforementioned formula (I) may form a salt. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine, δ -hydroxylysine, and arginine. When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid,

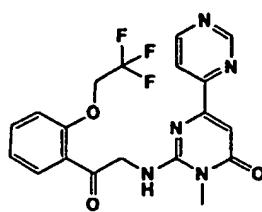
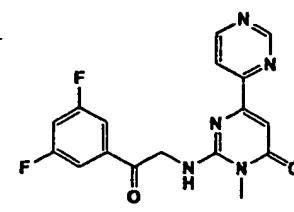
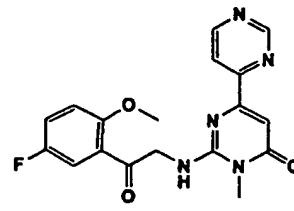
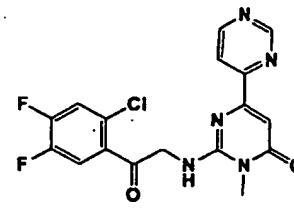
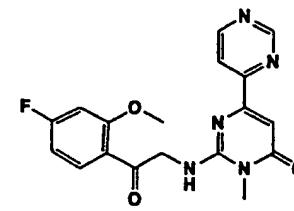
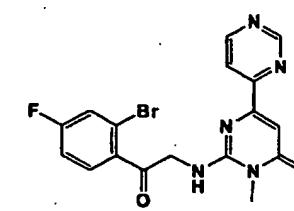
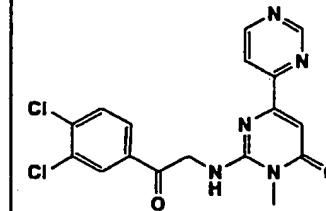
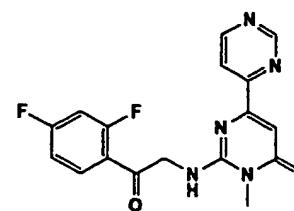
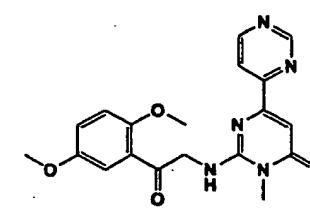
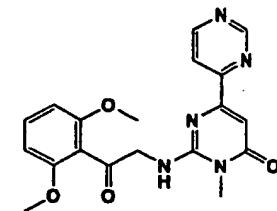
nicotinic acid, and salicylic acid; or salts with acidic amino acids such as aspartic acid, and glutamic acid.

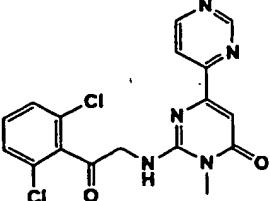
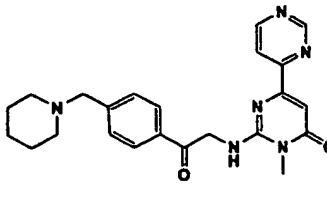
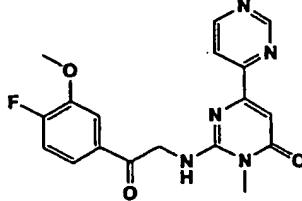
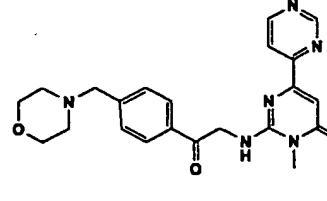
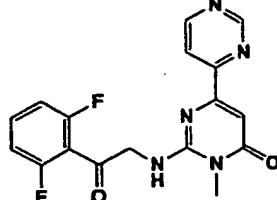
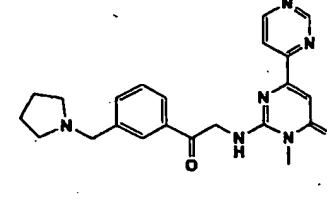
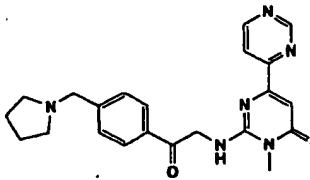
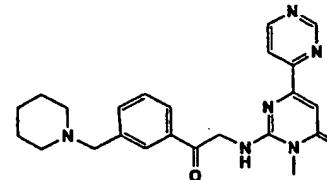
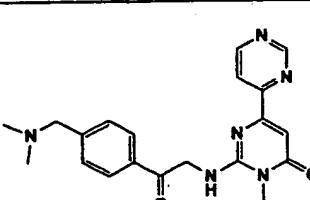
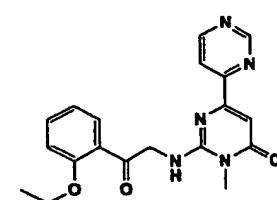
In addition to the 3-substituted-4-pyrimidone derivatives represented by the aforementioned formula (I) and salts thereof, their solvates and hydrates also fall within the scope of the present invention. The 3-substituted-4-pyrimidone derivatives represented by the aforementioned formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) and (S) configuration, and the pyrimidone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers of pure form, any mixtures of stereoisomers, racemates and the like fall within the scope of the present invention.

Examples of preferred compounds of the present invention are shown in the table below. However, the scope of the present invention is not limited by the following compounds.

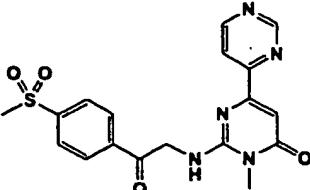
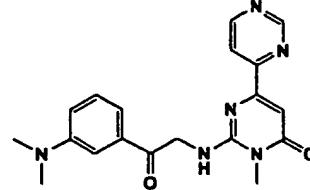
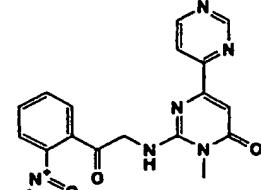
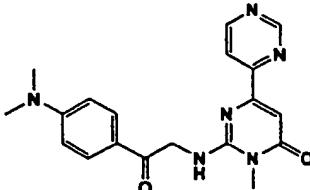
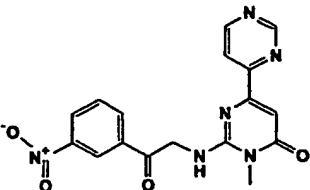
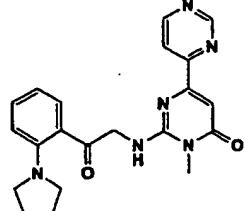
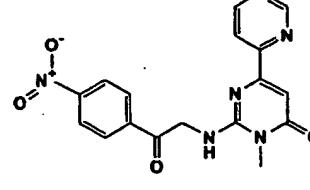
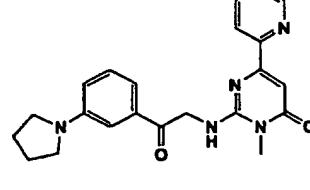
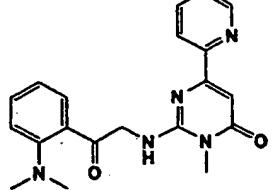
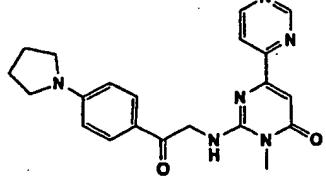
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A120		A126	
A121		A127	
A122		A128	
A123		A129	
A124		A130	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
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A132		A137	
A133		A138	
A134		A139	
A135		A140	

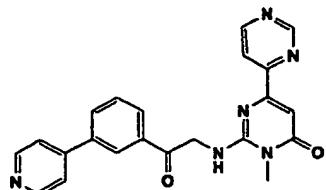
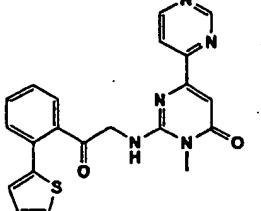
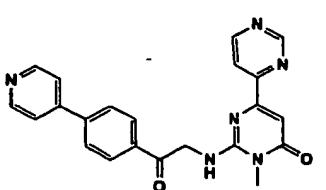
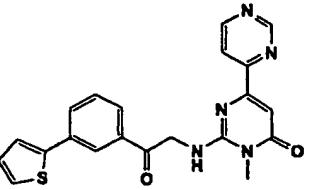
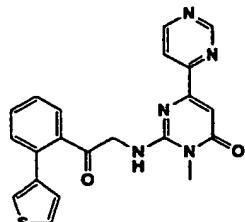
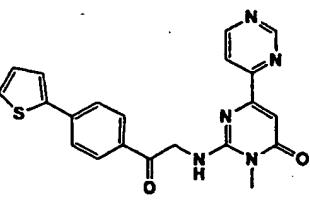
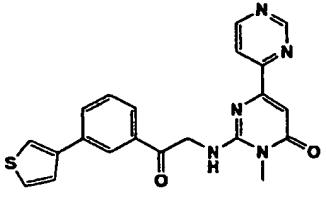
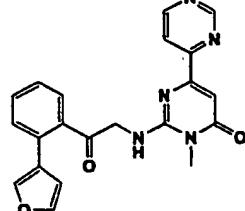
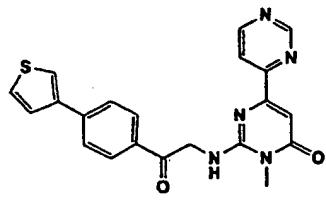
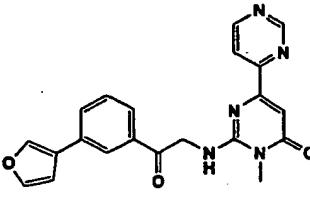
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A142		A147	
A143		A148	
A144		A149	
A145		A150	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
A151		A156	
A152		A157	
A153		A158	
A154		A159	
A155		A160	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
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A162		A167	
A163		A168	
A164		A169	
A165		A170	

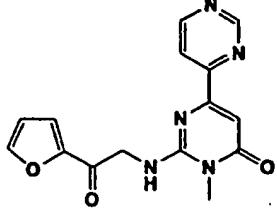
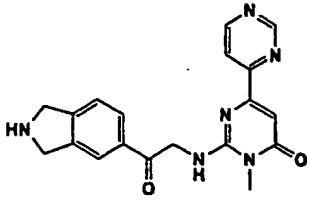
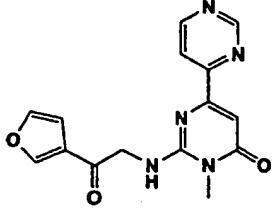
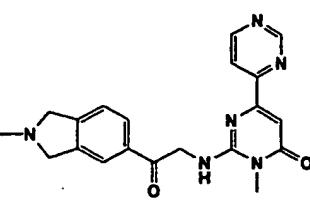
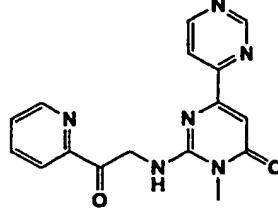
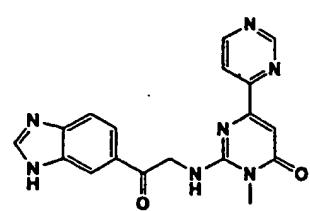
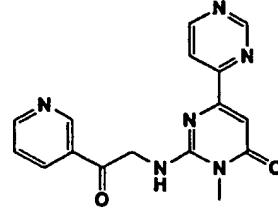
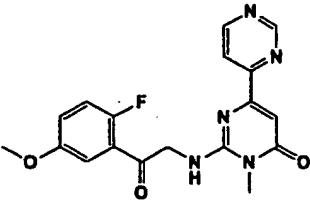
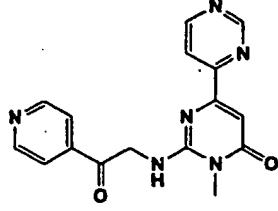
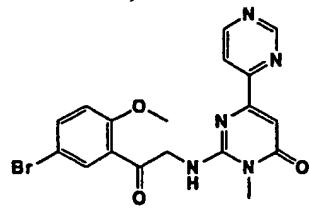
Compound No.	STRUCTURE	Compound No.	STRUCTURE
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A173		A178	
A174		A179	
A175		A180	

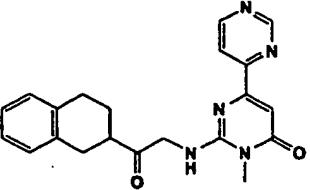
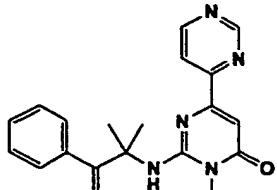
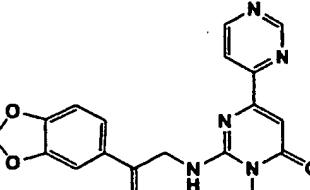
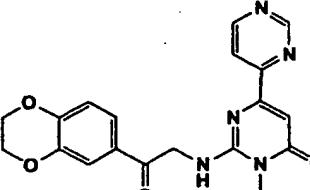
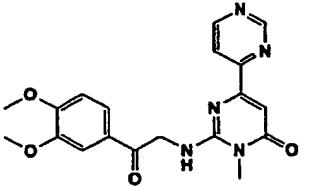
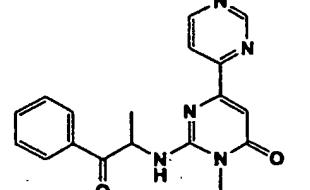
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A182		A187	
A183		A188	
A184		A189	
A185		A190	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
A191		A196	
A192		A197	
A193		A198	
A194		A199	
A195		A200	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
A201		A206	
A202		A207	
A203		A208	
A204		A209	
A205		A210	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
A211		A216	
A212		A217	
A213		A218	
A214		A219	
A215		A220	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
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A222		A227	
A223		A228	
A224		A229	
A225		A230	

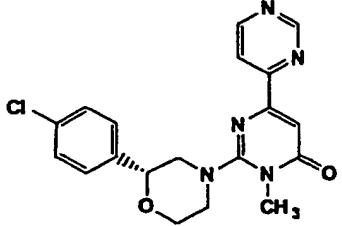
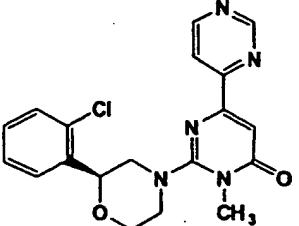
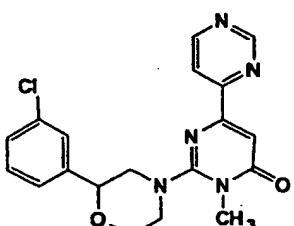
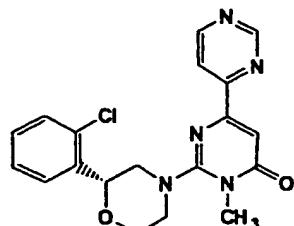
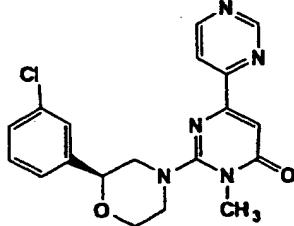
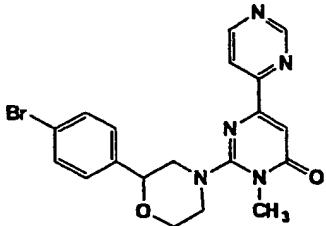
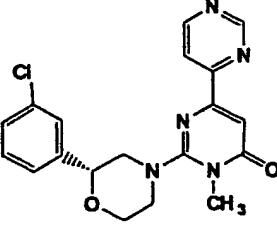
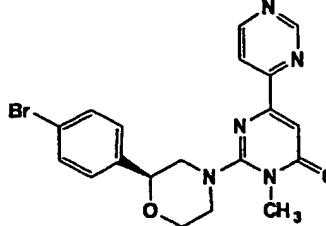
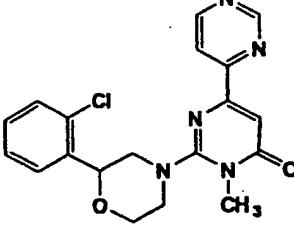
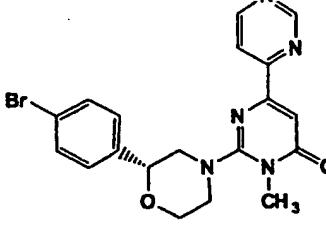
Compound No.	STRUCTURE	Compound No.	STRUCTURE
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A232			
A233			
A234			
A235			

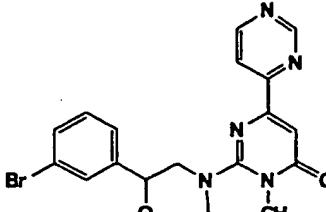
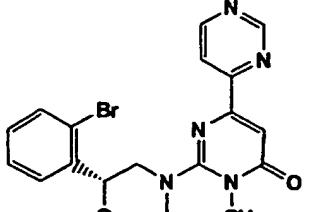
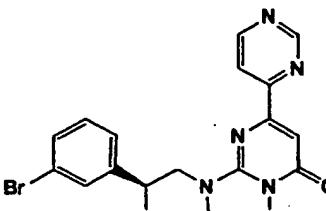
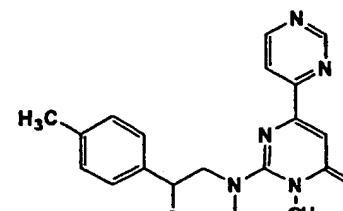
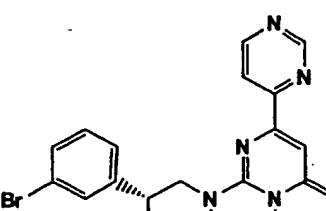
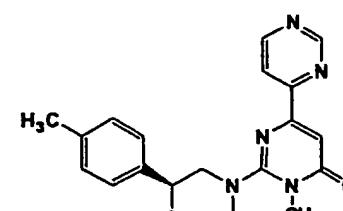
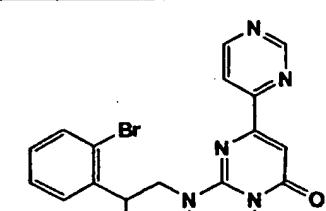
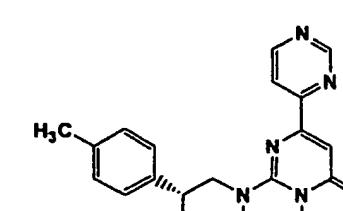
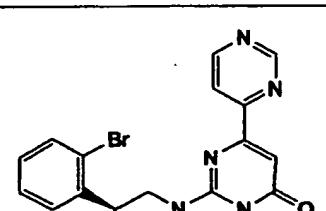
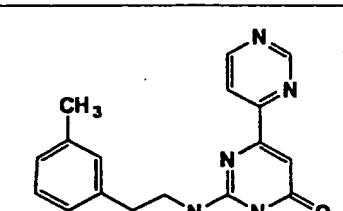
Compound No.	STRUCTURE	Compound No.	STRUCTURE
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B002		B007	
B003		B008	
B004		B009	
B005		B010	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
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B012		B017	
B013		B018	
B014		B019	
B015		B020	

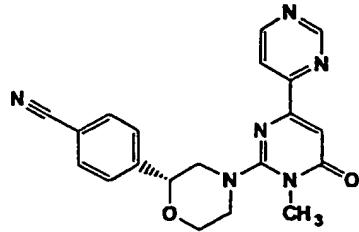
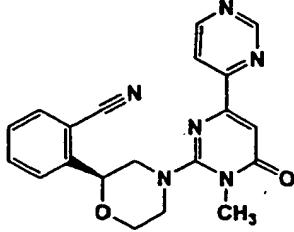
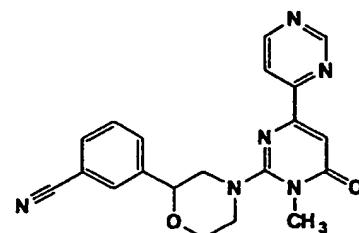
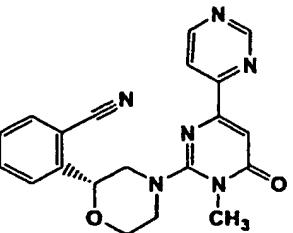
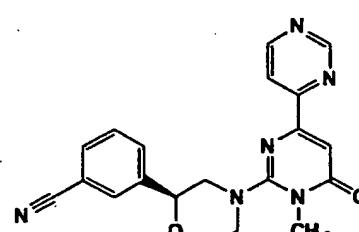
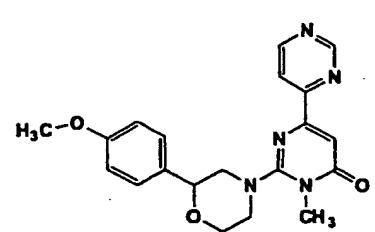
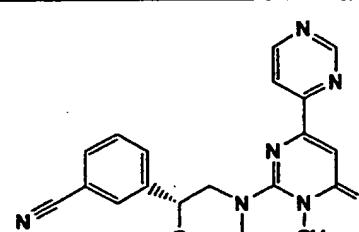
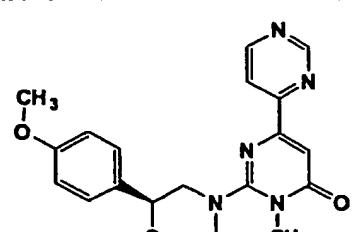
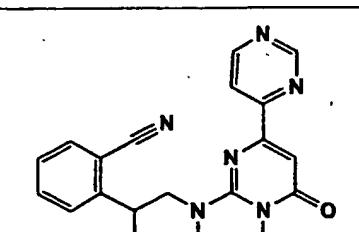
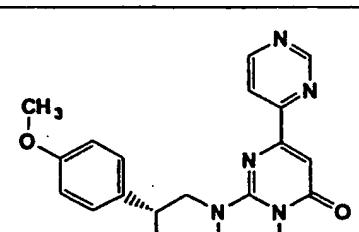
Compound No.	STRUCTURE	Compound No.	STRUCTURE
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B022		B027	
B023		B028	
B024		B029	
B025		B030	

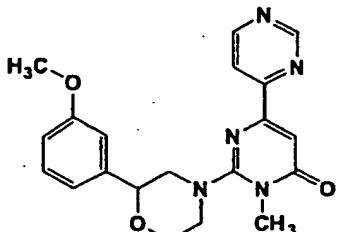
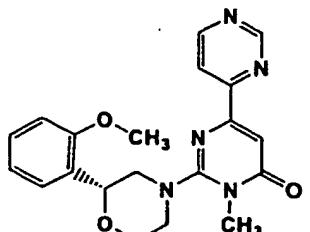
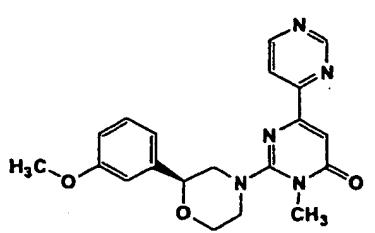
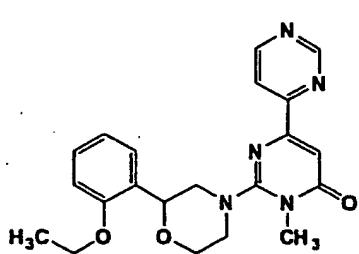
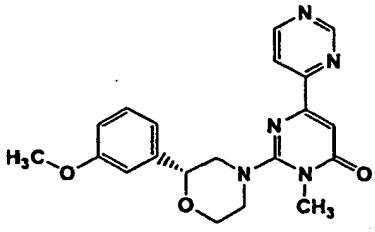
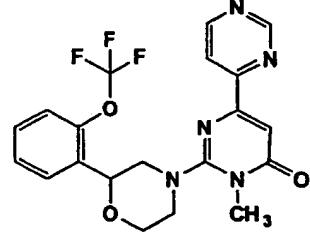
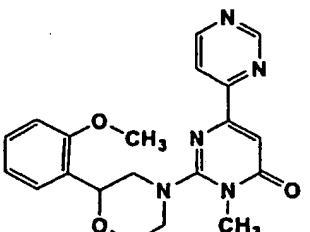
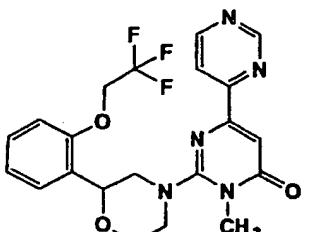
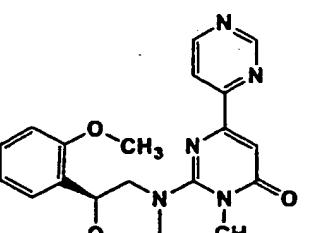
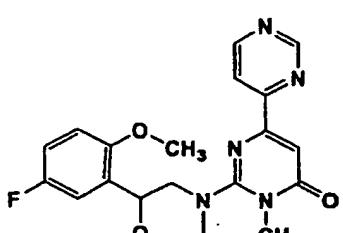
Compound No.	STRUCTURE	Compound No.	STRUCTURE
B031		B036	
B032		B037	
B033		B038	
B034		B039	
B035		B040	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B041		B046	
B042		B047	
B043		B048	
B044		B049	
B045		B050	

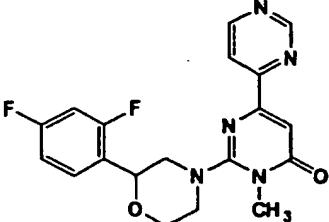
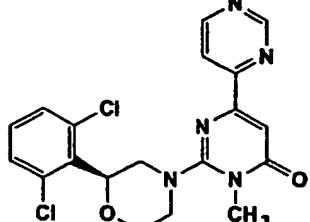
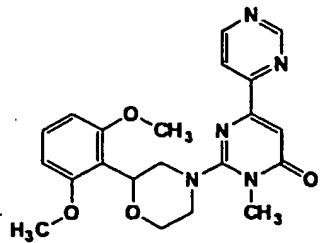
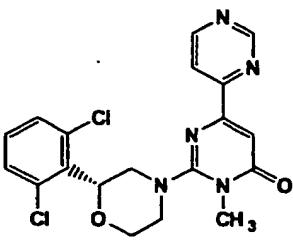
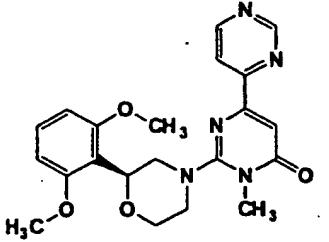
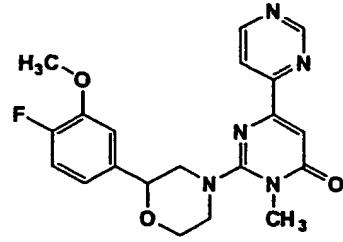
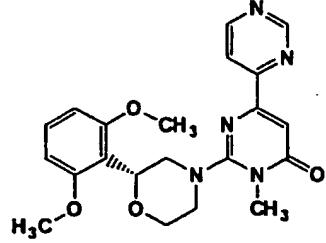
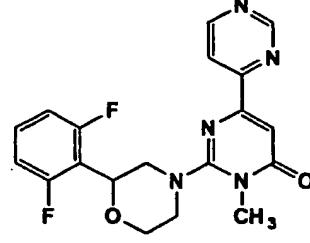
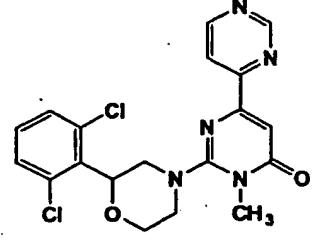
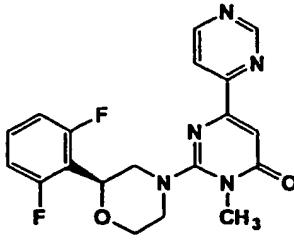
Compound No.	STRUCTURE	Compound No.	STRUCTURE
B051		B056	
B052		B057	
B053		B058	
B054		B059	
B055		B060	

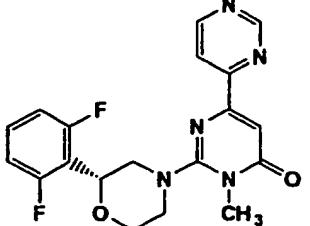
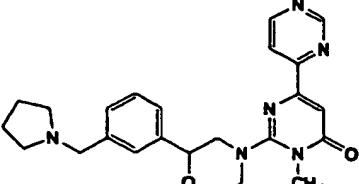
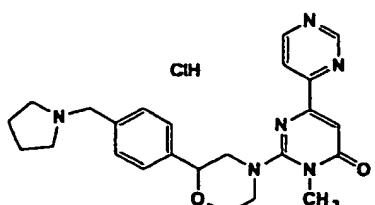
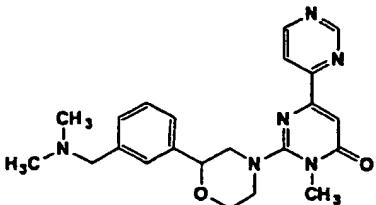
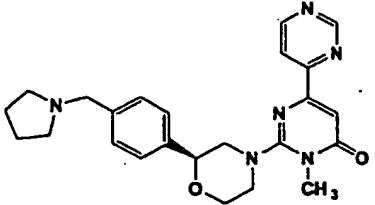
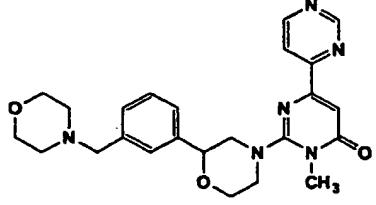
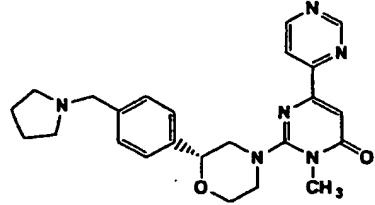
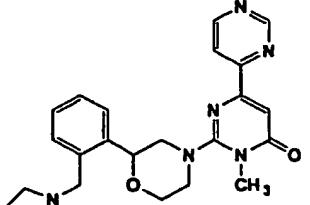
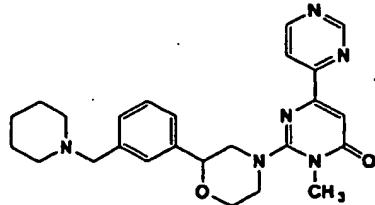
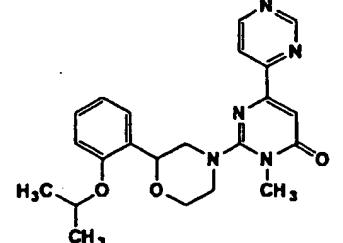
Compound No.	STRUCTURE	Compound No.	STRUCTURE
B061		B066	
B062		B067	
B063		B068	
B064		B069	
B065		B070	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B071		B076	
B072		B077	
B073		B078	
B074		B079	
B075		B080	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B081		B086	
B082		B087	
B083		B088	
B084		B089	
B085		B090	

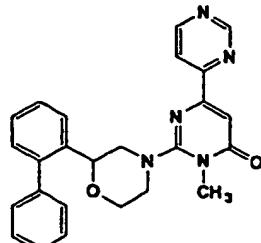
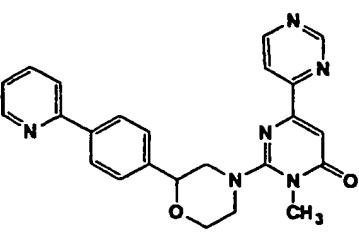
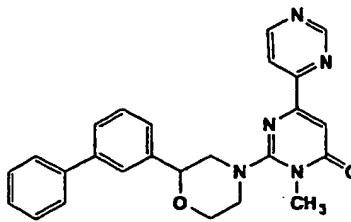
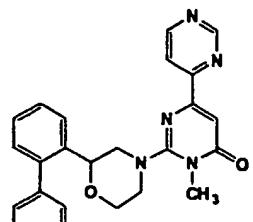
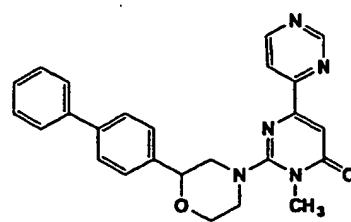
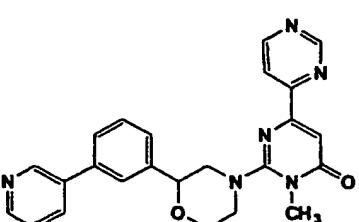
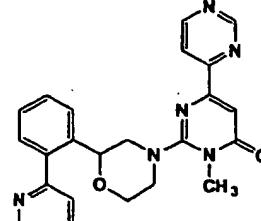
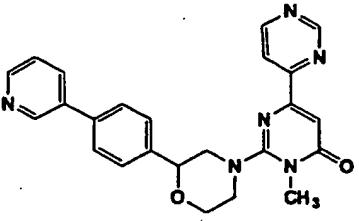
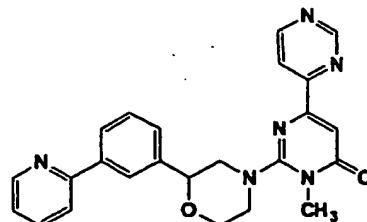
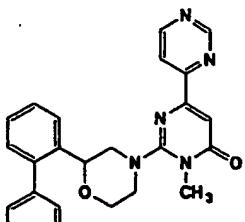
Compound No.	STRUCTURE	Compound No.	STRUCTURE
B091		B096	
B092		B097	
B093		B098	
B094		B099	
B095		B100	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B101		B106	
B102		B107	
B103		B108	
B104		B109	
B105		B110	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B111		B116	
B112		B117	
B113		B118	
B114		B119	
B115		B120	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B121		B126	
B122		B127	
B123		B128	
B124		B129	
B125		B130	

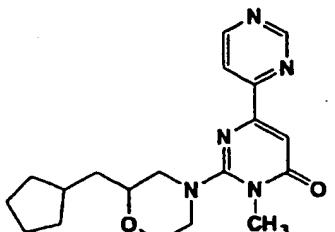
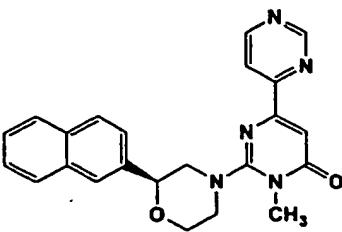
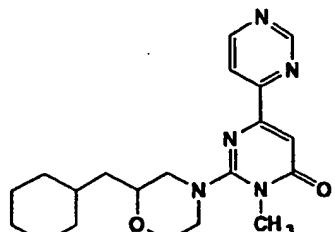
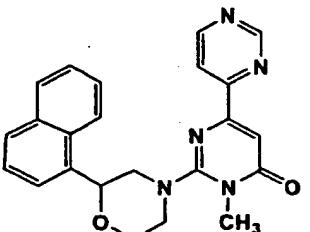
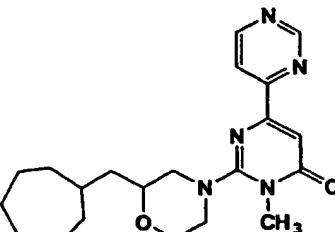
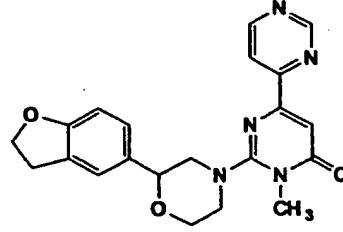
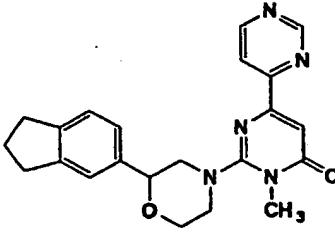
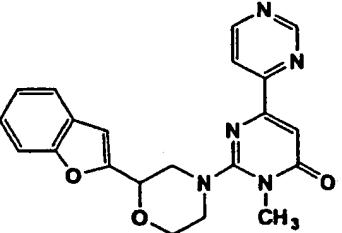
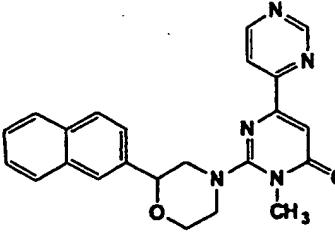
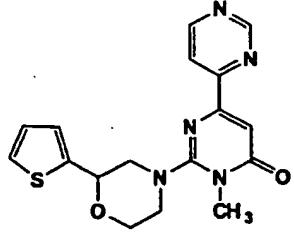
Compound No.	STRUCTURE	Compound No.	STRUCTURE
B131		B136	
B132		B137	
B133		B138	
B134		B139	
B135		B140	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B141		B146	
B142		B147	
B143		B148	
B144		B149	
B145		B150	

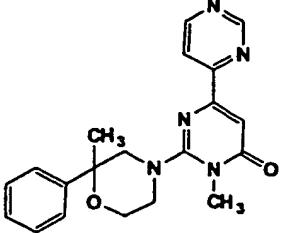
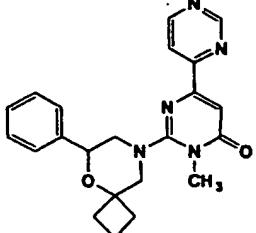
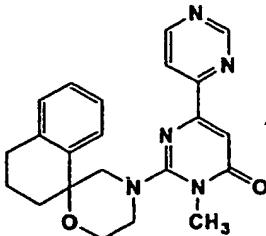
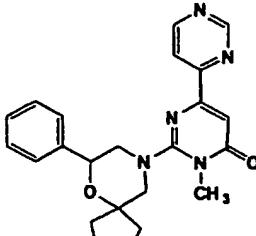
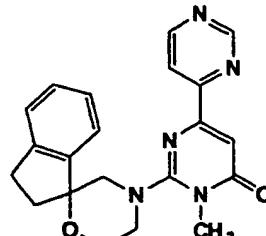
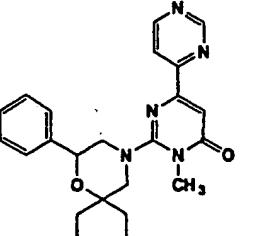
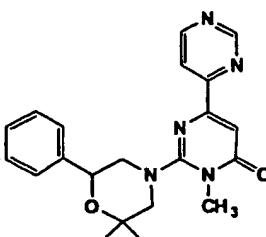
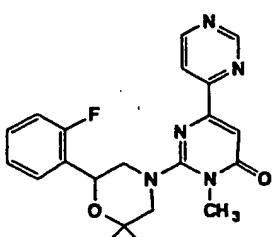
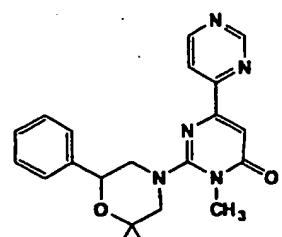
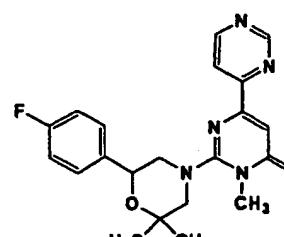
Compound No.	STRUCTURE	Compound No.	STRUCTURE
B151		B156	
B152		B157	
B153		B158	
B154		B159	
B155		B160	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B161		B166	
B162		B167	
B163		B168	
B164		B169	
B165		B170	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B171		B176	
B172		B177	
B173		B178	
B174		B179	
B175		B180	

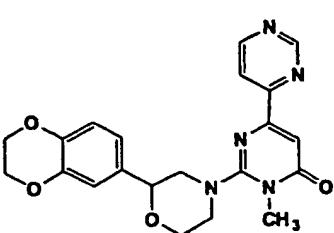
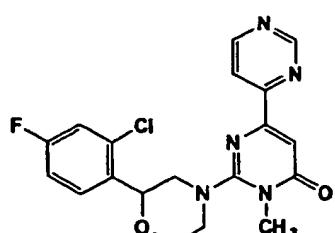
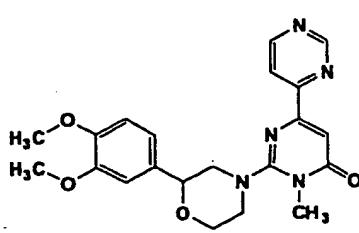
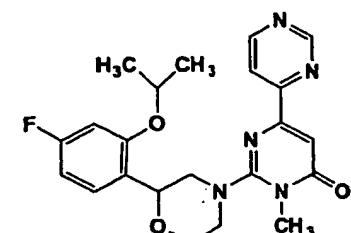
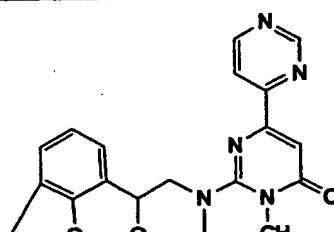
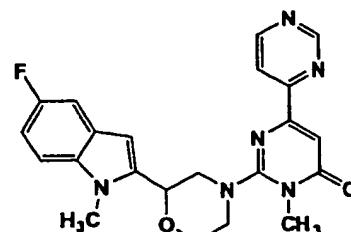
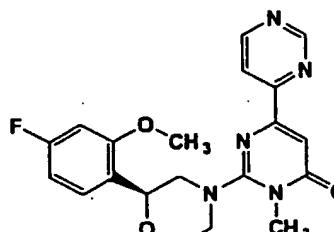
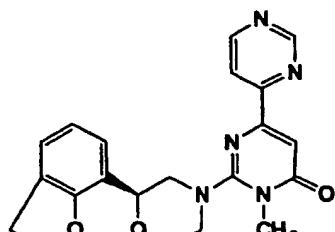
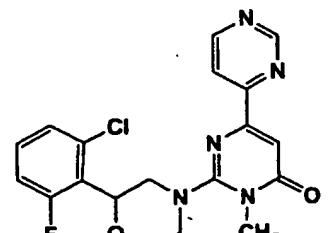
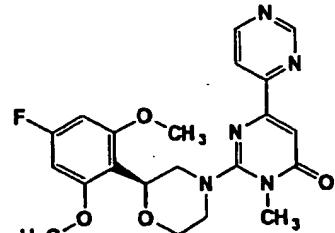
Compound No.	STRUCTURE	Compound No.	STRUCTURE
B181		B186	
B182		B187	
B183		B188	
B184		B189	
B185		B190	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B191		B196	
B192		B197	
B193		B198	
B194		B199	
B195		B200	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B201		B207	
B202		B208	
B203		B209	
B205		B213	
B206		B214	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B215		B220	
B216		B221	
B217		B222	
B218		B223	
B219		B224	

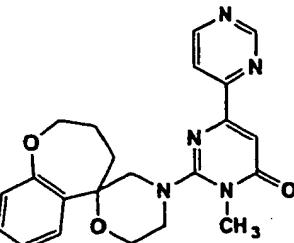
Compound No.	STRUCTURE	Compound No.	STRUCTURE
B225		B230	
B226		B231	
B227		B232	
B228		B233	
B229		B234	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B235		B240	
B236		B241	
B237		B242	
B238		B243	
B239		B244	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B245		B250	
B246		B251	
B247		B252	
B248		B253	
B249		B254	

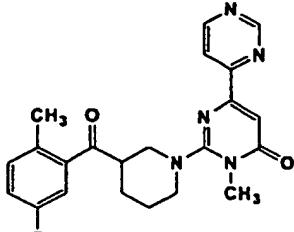
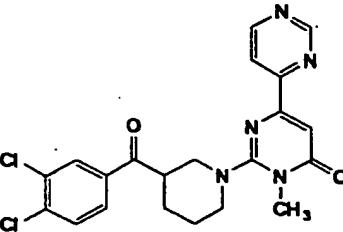
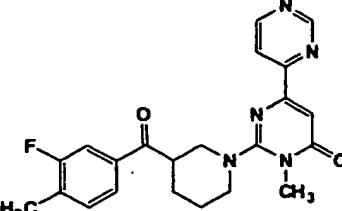
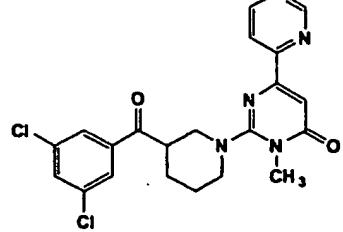
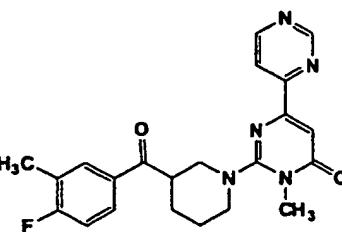
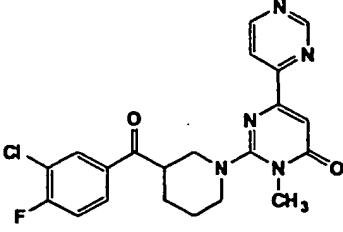
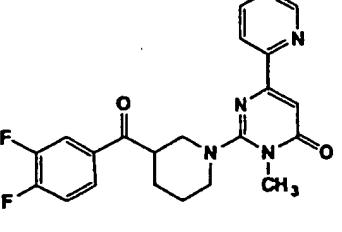
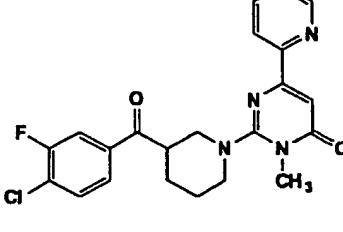
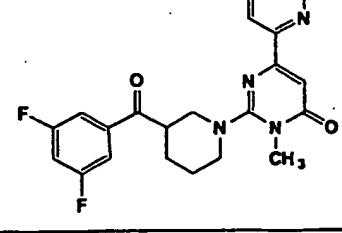
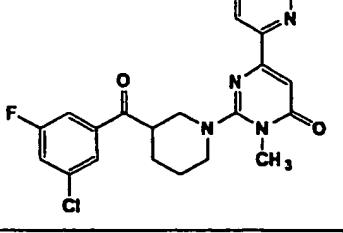
Compound No.	STRUCTURE	Compound No.	STRUCTURE
B255		B260	
B256		B261	
B257		B262	
B258		B263	
B259		B264	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B265		B270	
B266		B271	
B267		B272	
B268		B273	
B269		B274	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B285			

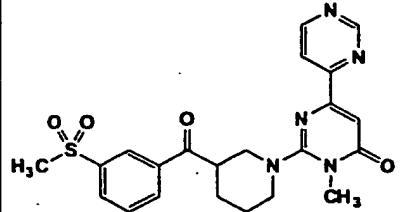
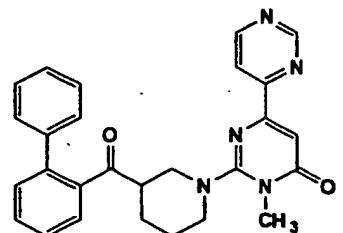
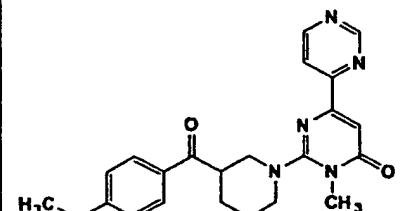
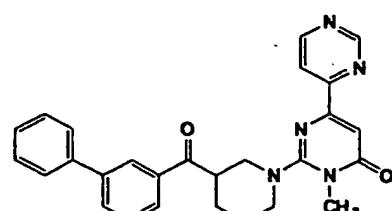
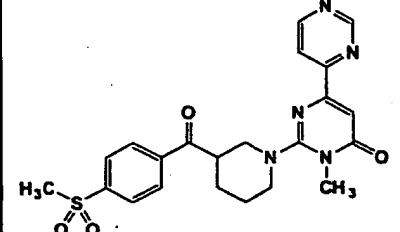
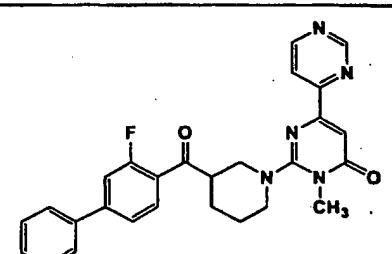
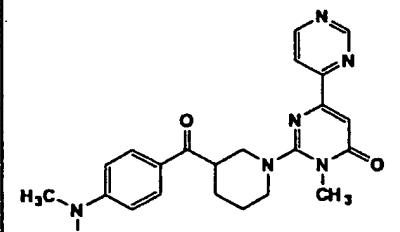
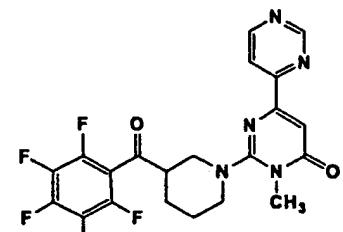
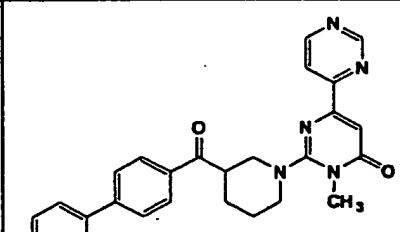
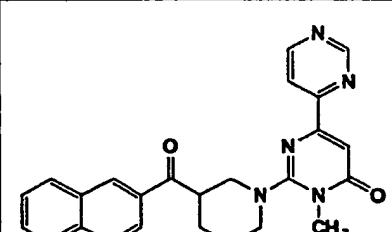
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C401		C406	
C402		C407	
C403		C408	
C404		C409	
C405		C410	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C411		C416	
C412		C417	
C413		C418	
C414		C419	
C415		C420	

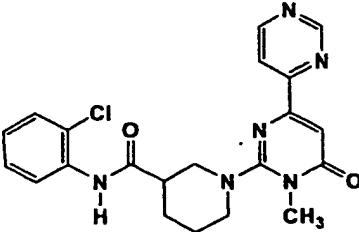
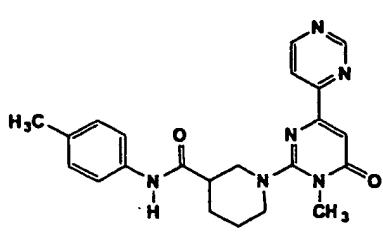
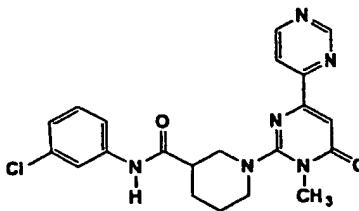
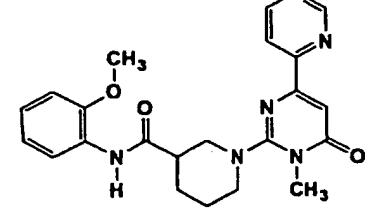
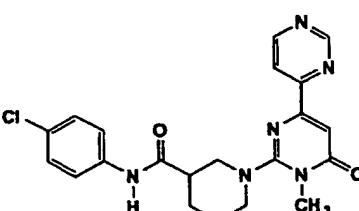
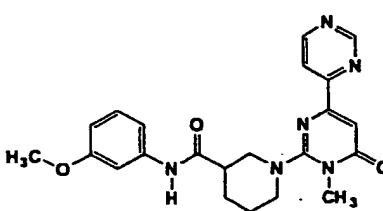
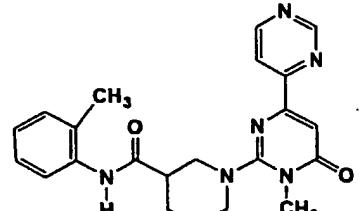
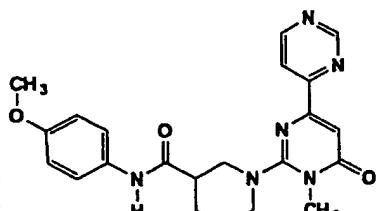
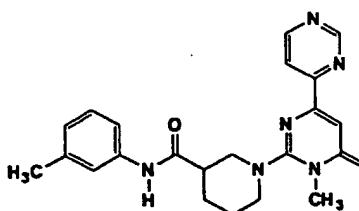
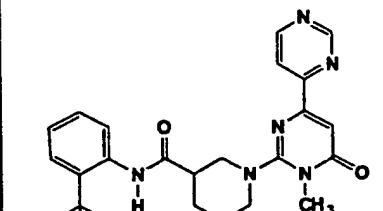
Compound No.	STRUCTURE	Compound No.	STRUCTURE
C421		C426	
C422		C427	
C423		C428	
C424		C429	
C425		C430	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C431		C436	
C432		C437	
C433		C438	
C434		C439	
C435		C440	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C441		C446	
C442		C447	
C443		C448	
C444		C449	
C445		C450	

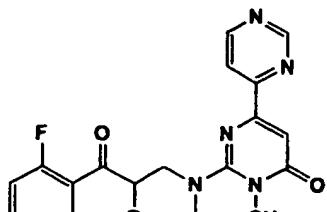
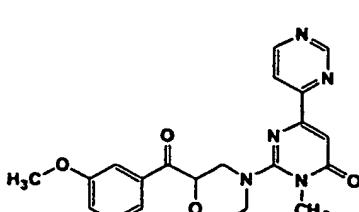
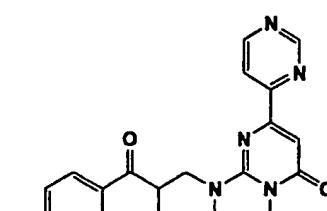
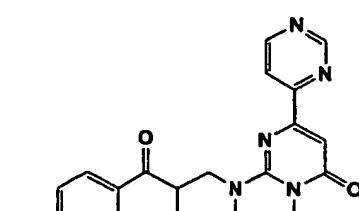
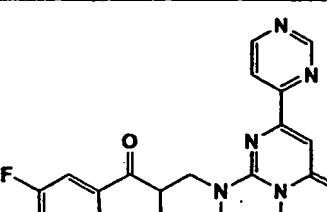
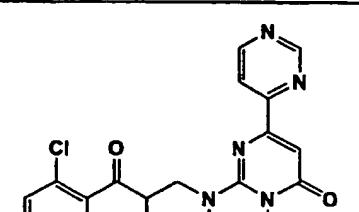
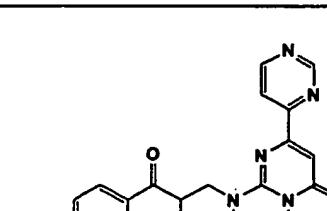
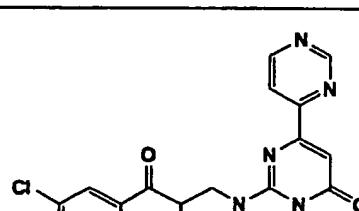
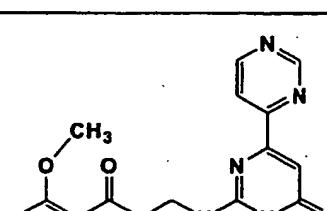
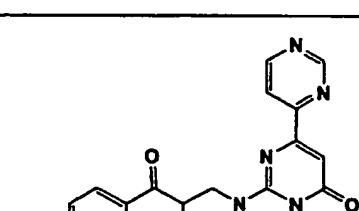
Compound No.	STRUCTURE	Compound No.	STRUCTURE
C451		C456	
C452		C457	
C453		C458	
C454		C459	
C455		C460	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C461		C466	
C462		C467	
C463		C468	
C464		C469	
C465		C470	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C471		C476	
C472		C477	
C473		C478	
C474		C479	
C475		C480	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C481		C486	
C482		C487	
C483		C488	
C484		C489	
C485		C490	

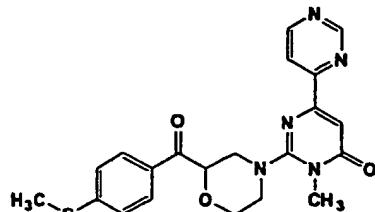
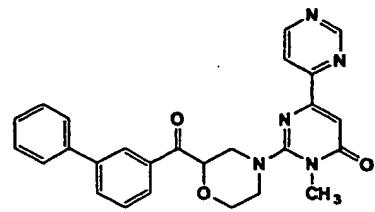
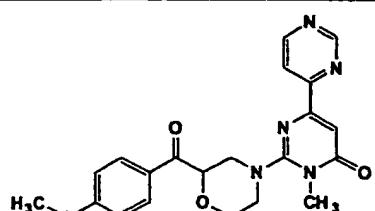
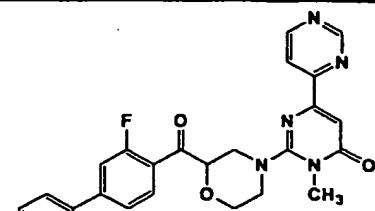
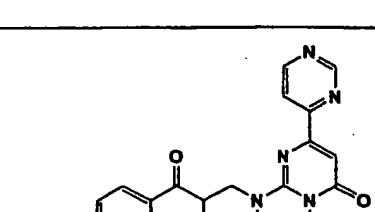
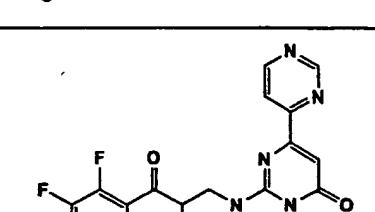
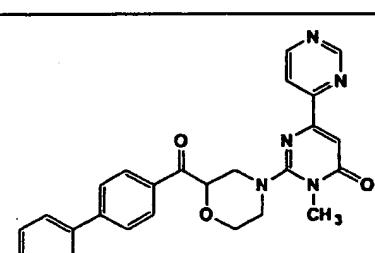
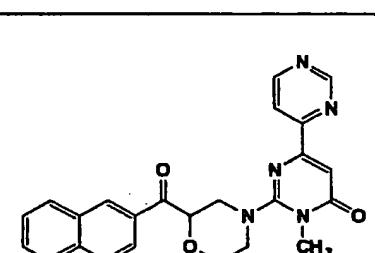
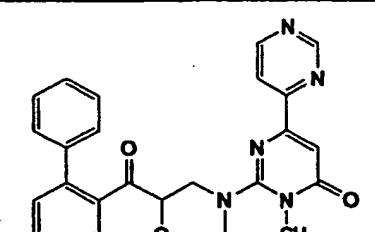
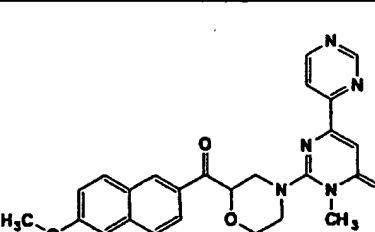
Compound No.	STRUCTURE	Compound No.	STRUCTURE
C491		C496	
C492		C497	
C493		C498	
C494		C499	
C495		C501	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C502		C507	
C503		C508	
C504		C509	
C505		C510	
C506		C511	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C512		C517	
C513		C518	
C514		C519	
C515		C520	
C516		C521	

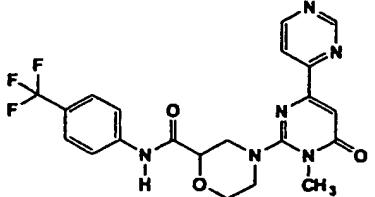
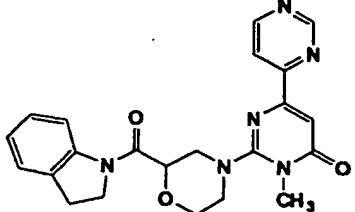
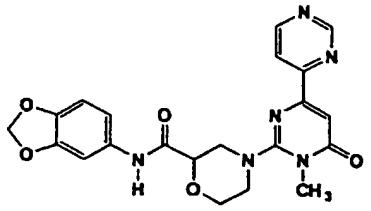
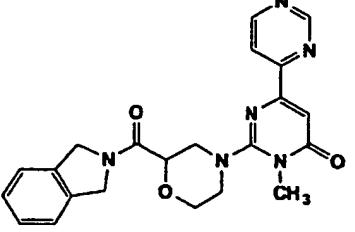
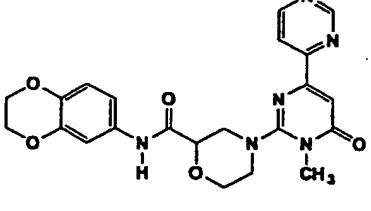
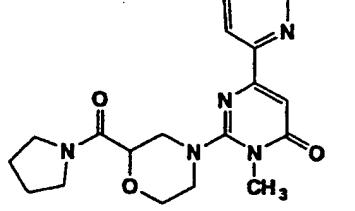
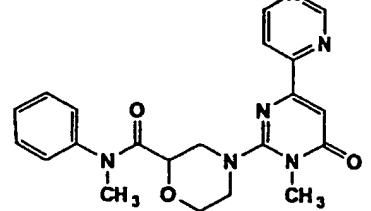
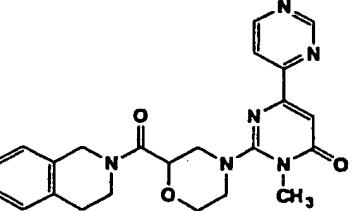
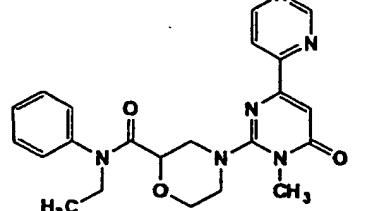
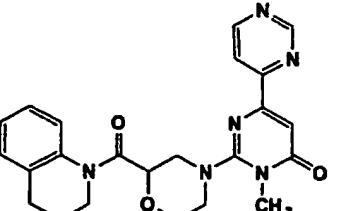
Compound No.	STRUCTURE	Compound No.	STRUCTURE
C532		C537	
C533		C538	
C534		C539	
C535		C540	
C536		C541	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C542		C547	
C543		C548	
C544		C549	
C545		C550	
C546		C551	

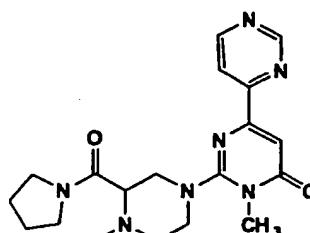
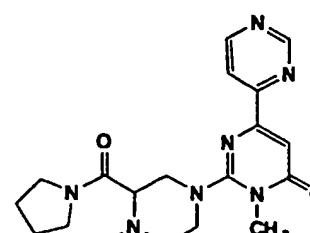
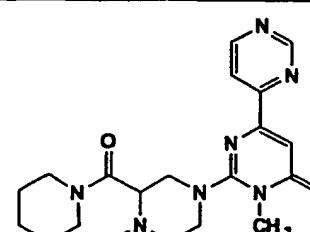
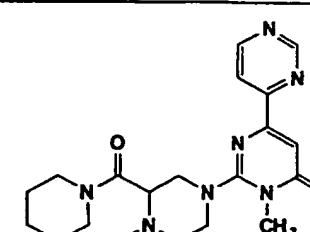
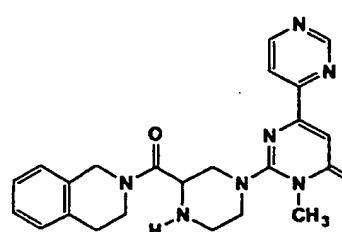
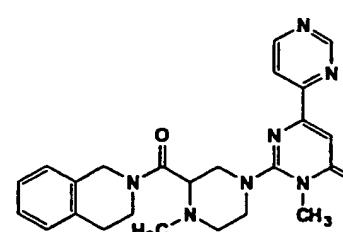
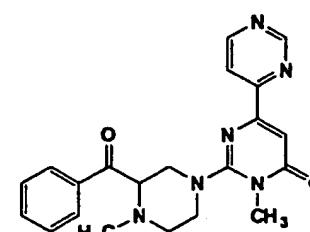
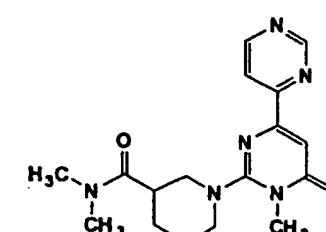
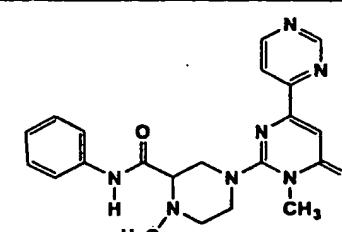
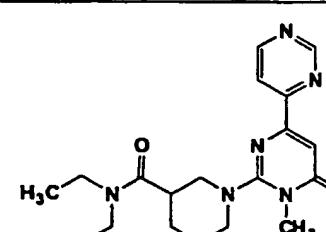
Compound No.	STRUCTURE	Compound No.	STRUCTURE
C552		C557	
C553		C558	
C554		C559	
C555		C560	
C556		C561	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C562		C567	
C563		C568	
C564		C569	
C565		C570	
C566		C571	

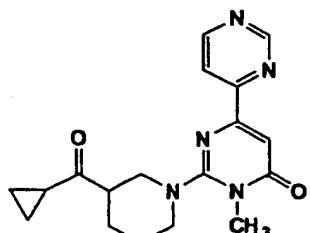
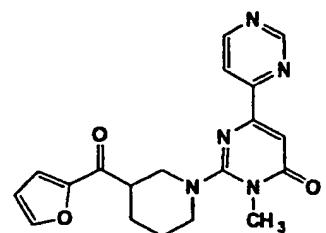
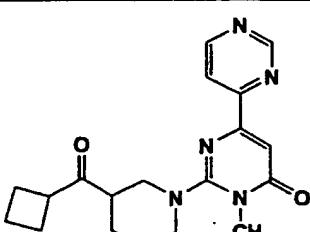
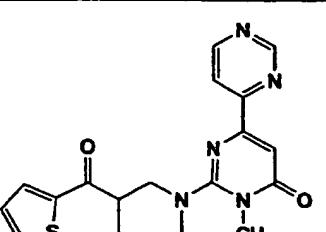
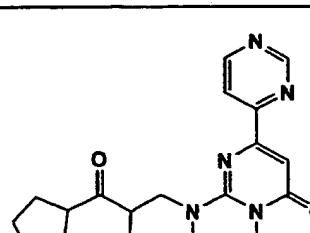
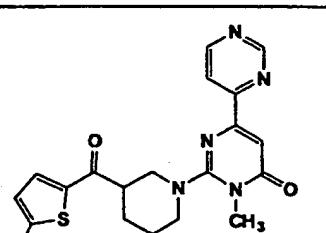
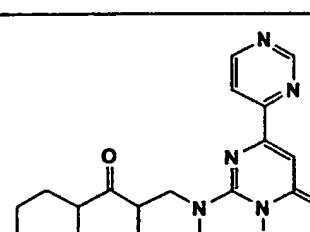
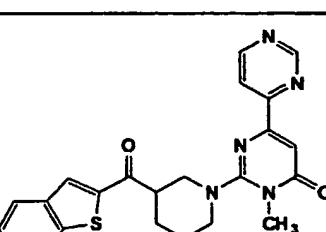
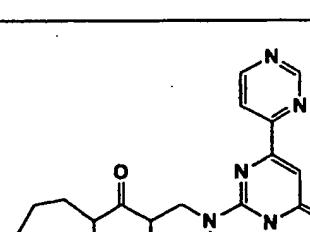
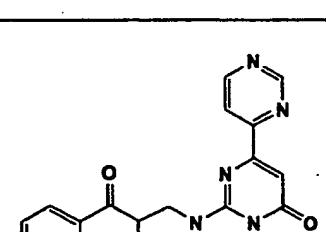
Compound No.	STRUCTURE	Compound No.	STRUCTURE
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C573		C578	
C574		C579	
C575		C580	
C576		C581	

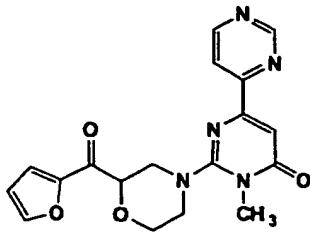
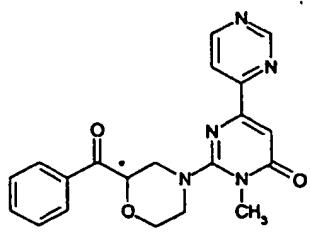
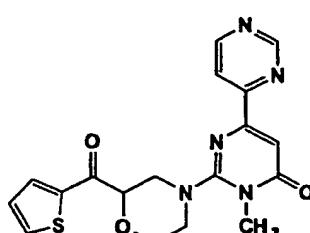
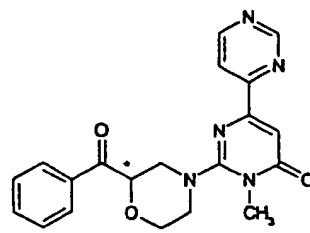
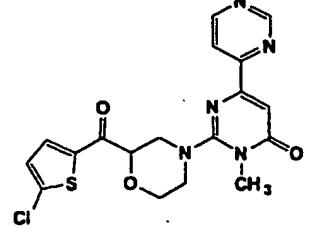
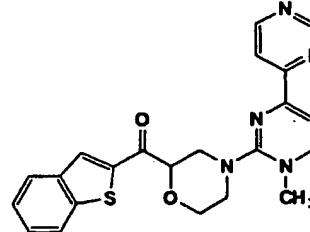
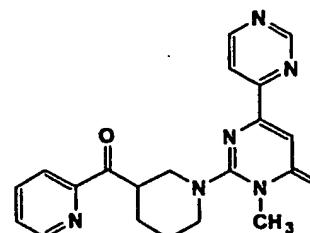
Compound No.	STRUCTURE	Compound No.	STRUCTURE
C582		C587	
C583		C588	
C584		C589	
C585		C590	
C586		C591	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C592		C597	
C593		C598	
C594		C599	
C595		C601	
C596		C602	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C603		C608	
C604		C609	
C605		C610	
C606		C650	
C607		C651	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C660		754	
C661		C755	
C751		C756	
C752		C757	
C753		C758	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C759		C764	
C760		C765	
C761		C766	
C762		C767	
C763		C768	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
C784		C789	
C785		C790	
C786			
C787			
C788			

Compound No.	STRUCTURE	Compound No.	STRUCTURE
D026		D031	
D027		D032	
D028		D033	
D029		D034	
D030		D035	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
D036		D041	
D037		D042	
D038		D043	
D039		D044	
D040		D045	

Compound No.	STRUCTURE		
D046			
D047			
D048			
D049			
D050			

Compound B275 and B276

• Measurement condition

CHIRALPAK AD

Mobile phase: n-hexane : i-propanol = 80 : 20

Flow rate: 1.0 ml/min

Temperature: 30°C

• Retention time

B275: 19.1 min

B276: 21.5 min

Compound C789 and C790

• Measurement condition

CHIRALPAK AD

Mobile phase: n-hexane : i-propanol = 60 : 40

Flow rate: 1.0 ml/min

Temperature: 30°C

• Retention time

B789: 17.7 min

B790: 14.0 min

Particularly preferred compounds of the present invention represented by

formula (I) include:

3-methyl-2-(2-oxo-2-phenylethylamino)-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

3-methyl-2-(2-oxo-2-(3-fluorophenyl)ethylamino)-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

3-methyl-2-(2-oxo-2-(4-fluorophenyl)ethylamino)-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

3-methyl-2-(2-oxo-2-(3-chlorophenyl)ethylamino)-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

3-methyl-2-(2-oxo-2-(3-methylphenyl)ethylamino)-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(4-Fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
(S)-2-[2-(4-Fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2-Fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
(S)-2-[2-(2-Fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(4-Chlorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
2-[2-(3-Chlorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
2-[2-(2-Chlorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
(S)-2-[2-(2-Chlorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(4-Bromophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
(S)-2-[2-(4-Bromophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(3-Bromophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
(S)-2-[2-(3-Bromophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2-Bromophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
2-[2-(4-Methylphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
2-[2-(3-Methylphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
2-[2-(2-Methylphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
(S)-2-[2-(2-Methylphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(4-Cyanophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
2-[2-(3-Cyanophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(*S*)-2-[2-(3-Cyanophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(2-Cyanophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;
2-[2-(4-Methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

(*S*)-2-[2-(4-Methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(3-Methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

(*S*)-2-[2-(3-Methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(2-Methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

(*S*)-2-[2-(2-Methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(2-Ethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(2-Trifluoromethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(5-Fluoro-2-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(4-Fluoro-2-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

(*S*)-2-[2-(4-Fluoro-2-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(2,5-Dimethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

(*S*)-2-[2-(2,5-Dimethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-

pyrimidin-4-one;

2-[2-(2-Chloro-4,5-difluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2-Chloro-4,5-difluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2-Bromo-4-fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2,4-Difluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2,4-Difluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2,6-Dimethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2,6-Dimethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2,4-Dimethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2,4-Dimethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2,6-Dichlorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2,6-Dichlorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2,6-Difluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2,6-Difluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2-Chloro-6-fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

(S)-2-[2-(2-Chloro-6-fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(4-Fluoro-3-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(5-Cyano-2-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

(S)-2-[2-(5-Cyano-2-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(4-Cyano-2-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

(S)-2-[2-(4-Cyano-2-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(2,4-Difluoro-6-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

(S)-2-[2-(2,4-Difluoro-6-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(4-(Pyrrolidin-1-yl-methyl)phenyl)morpholino-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

(S)-2-[2-(4-(Pyrrolidin-1-yl-methyl)phenyl)morpholino-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(1-Naphthyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(2-Naphthyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

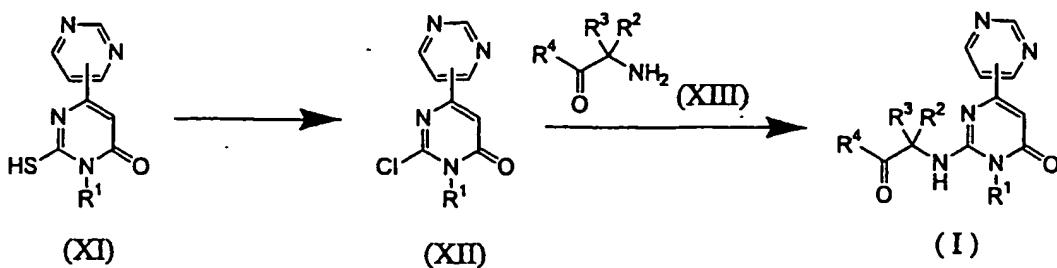
(S)-2-[2-(2-Naphthyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

2-[2-(2,3-Dihydrobenzofuran-7-yl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

(S)-2-[2-(2,3-Dihydrobenzofuran-7-yl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3 H-pyrimidin-4-one; 2-[2-(Benzofuran-2-yl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3 H-pyrimidin-4-one; (S)-2-[2-(Benzofuran-2-yl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3 H-pyrimidin-4-one; 2-[3-(4-Fluorobenzoyl)piperidin-1-yl]-3-methyl-6-pyrimidin-4-yl-3 H-pyrimidin-4-one; 2-(3-Benzoylpiperidin-1-yl)-3-methyl-6-pyrimidin-4-yl-3 H-pyrimidin-4-one; 2-[3-(2-Methoxybenzoyl)piperidin-1-yl]-3-methyl-6-pyrimidin-4-yl-3 H-pyrimidin-4-one; 2-[3-(4-Methoxybenzoyl)piperidin-1-yl]-3-methyl-6-pyrimidin-4-yl-3 H-pyrimidin-4-one; 2-[2-(4-Fluorobenzoyl)morpholine-4-yl]-3-methyl-6-pyrimidin-4-yl-3 H-pyrimidin-4-one; 2-(2-Benzoylmorpholine-4-yl)-3-methyl-6-pyrimidin-4-yl-3 H-pyrimidin-4-one; 2-[2-(2-Methoxybenzoyl)morpholine-4-yl]-3-methyl-6-pyrimidin-4-yl-3 H-pyrimidin-4-one; and 2-[2-(4-Methoxybenzoyl)morpholine-4-yl]-3-methyl-6-pyrimidin-4-yl-3 H-pyrimidin-4-one; and 2-[4-(4-Chlorobenzoyl)piperidin-1-yl]-3-methyl-6-pyrimidin-4-yl-3 H-pyrimidin-4-one.

Salts of the aforementioned preferred compound, and solvates or hydrates of the aforementioned compounds and salts thereof are also preferred.

The 3-substituted-4-pyrimidone compounds represented by the aforementioned formula (I) wherein R is the group represented by formula (II) can be prepared, for example, according to the method explained below.



(In the above scheme, definitions of R¹, R², R³ and R⁴ are the same as those already described.)

The 2-thiopyrimidone represented by the above formula (XI) is prepared easily by a modification of the method described in EP 354,179. The reaction is carried out in the presence of a base such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, triethylamine, diisopropylethylamine, and 1,8-diazabicyclo[5.4.0]undec-7-en for 1 to 100 hours at a suitable temperature ranging from 0°C to 200°C under nitrogen or argon atmosphere or under ordinary air to afford the desired compound (XI). Examples of a solvent for the reactions include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol, ethylene glycol, propylene glycol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene, toluene, xylene; halogenated hydrocarbonic solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide, water and the like. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used.

Then the 2-thiopyrimidone derivative (XI) is transformed into the 2-chloropyrimidone (XII) by a chlorinating agent. The reaction time and

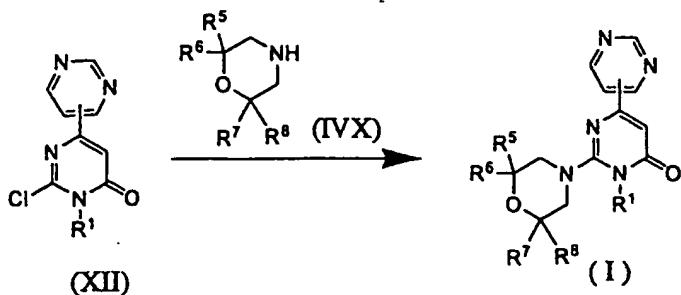
temperature depend on the chlorinating agent used. Examples of a chlorinating agent for the reactions include, for example, thionyl chloride, thionyl chloride and dimethylformamide, phosphorus oxychloride, phosphorus oxychloride and dimethylformamide, oxalyl chloride, phosphorous oxychloride and dimethylformamide, and phosphorus pentachloride.

The amine represented by the above formula (XIII) or salts thereof is may be prepared by a modification of the method described in the literature (Tetrahedron Lett., 30, 5285 (1989), Synthesis, 122 (1990)).

Then the chloride derivative (XII) is allowed to react with the amine (XIII) or salts thereof in the presence of a base such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, triethylamine, diisopropylethylamine, and 1,8-diazabicyclo[5.4.0]undec-7-en for 1 to 100 hours at a suitable temperature ranging from 0°C to 200°C under nitrogen or argon atmosphere or under ordinary air to afford the desired compound (I). 4-Dimethylaminopyridine may be used as a catalyst.

Examples of a solvent for the reactions include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol, ethylene glycol, propylene glycol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene, toluene, xylene; halogenated hydrocarbonic solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide, water and the like. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used.

The 3-substituted-4-pyrimidone compounds represented by the aforementioned formula (I) wherein R is the group represented by formula (III) can be prepared, for example, according to the method explained below.

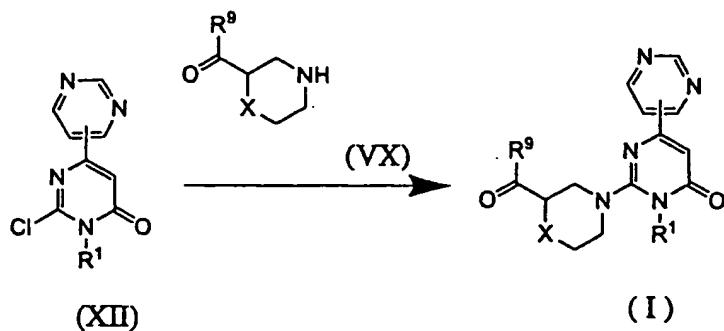


(In the above scheme, definitions of R¹, R⁵, R⁶, R⁷ and R⁸ are the same as those already described.)

The chloride derivative (XII) is allowed to react with the amine (IVX) or salts thereof in the presence of a base such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, triethylamine, diisopropylethylamine, and 1,8-diazabicyclo[5.4.0]undec-7-en for 1 to 100 hours at a suitable temperature ranging from 0°C to 200°C under nitrogen or argon atmosphere or under ordinary air to afford the desired compound (I).

Examples of a solvent for the reactions include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol, ethylene glycol, propylene glycol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene, toluene, xylene; halogenated hydrocarbonic solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide, water and the like. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used.

The 3-substituted-4-pyrimidone compounds represented by the aforementioned formula (I) wherein R is the group represented by formula (IV) can be prepared, for example, according to the method explained below.



(In the above scheme, definitions of R¹, R⁹, and X are the same as those already described.)

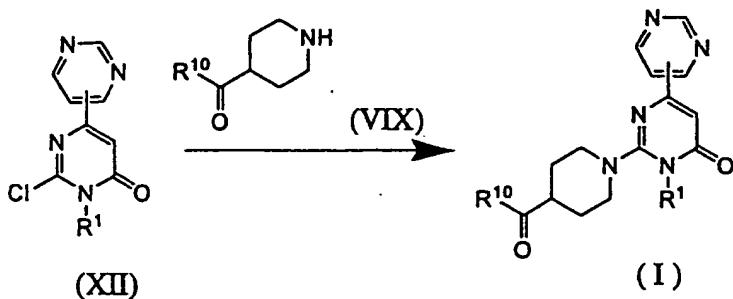
The amine represented by the above formula (VX) may be prepared by a modification of the method described in the literature (J. Med. Chem., 13, 1 (1970), J. Med. Chem., 41, 591 (1998)) or according to well-known methods of one skilled in the art.

Then the chloride derivative (XII) is allowed to react with the amine (VX) or salts thereof in the presence of a base such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, triethylamine, diisopropylethylamine, and 1,8-diazabicyclo[5.4.0]undec-7-en for 1 to 100 hours at a suitable temperature ranging from 0°C to 200°C under nitrogen or argon atmosphere or under ordinary air to afford the desired compound (I).

Examples of a solvent for the reactions include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol, ethylene glycol, propylene glycol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene, toluene, xylene; halogenated hydrocarbonic solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide,

N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide, water and the like. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used.

The 3-substituted-4-pyrimidone compounds represented by the aforementioned formula (I) wherein R is the group represented by formula (V) can be prepared, for example, according to the method explained below.



(In the above scheme, definitions of R¹ and R¹⁰ are the same as those already described.)

The amine represented by the above formula (VIX) is commercially available or may be prepared by a modification of the method described in the literature (J. Med. Chem., 13, 1 (1970), J. Med. Chem., 41, 591 (1998)) or according to well-known methods of one skilled in the art.

Then the chloride derivative (XII) is allowed to react with the amine (VIX) or salts thereof in the presence of a base such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, triethylamine, diisopropylethylamine, and 1,8-diazabicyclo[5.4.0]undec-7-en for 1 to 100 hours at a suitable temperature ranging from 0°C to 200°C under nitrogen or argon atmosphere or under ordinary air to afford the desired compound (I).

Examples of a solvent for the reactions include, for example, alcoholic solvent

such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol, ethylene glycol, propylene glycol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene, toluene, xylene; halogenated hydrocarbonic solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide, water and the like. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used.

The compounds of the present invention have inhibitory activity against TPK1, and they inhibit TPK1 activity in neurodegenerative diseases such as Alzheimer disease, thereby suppress the neurotoxicity of A β and the formation of PHF and inhibit the nerve cell death. Accordingly, the compounds of the present invention are useful as an active ingredient of a medicament which radically enables preventive and/or therapeutic treatment of Alzheimer disease. In addition, the compounds of the present invention are also useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitis, postencephalitic parkinsonism, pugilistic encephalosis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration frontotemporal dementia, vascular dementia, traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma, non-insulin dependent diabetes, obesity, manic depressive illness, schizophrenia, alopecia, breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia, and several virus-induced tumors.

As the active ingredient of the medicament of the present invention, a substance may be used which is selected from the group consisting of the compound

represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The substance, per se, may be administered as the medicament of the present invention, however, it is desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more of pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substance may be used in combination. The above pharmaceutical composition may be supplemented with an active ingredient of other medicament for the treatment of Alzheimer disease and the above-mentioned diseases.

A type of the pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content ratios of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic

substances, or solid or liquid substances may be used as pharmaceutical additives. Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1% by weight to 90% by weight based on the weight of an active ingredient.

Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for suppositories include, for example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

Dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a disease and the like. Generally, a daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

Examples

The present invention will be explained more specifically with reference to examples. However, the scope of the present invention is not limited to the following examples. The compound number in the examples corresponds to that in the table above.

Example 1: Synthesis of 2-mercaptop-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one

A solution of ethyl 3-oxo-3-(4-pyrimidyl)propionate (34.1 g, 176 mmol), N-methylthiourea (47.5 g, 527 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (26.3 ml, 176 mmol) in ethanol(340ml) was refluxed for 2 hours and the solution of methanesulfonic acid (16.9 g, 176 mmol) in water (70 ml) was added after cooling by ice-water. The precipitate was washed with water, filtered and dried to give the title compound (30.2 g, 78%).

¹H-NMR (DMSO-d₆) δ : 3.56(s, 3H), 6.88(s, 1H), 8.24(dd, J=1.2, 5.4Hz, 1H), 9.05(d, J=5.4Hz, 1H), 9.38(s, 1H), 11.94(s, 1H).

MS[M-H]⁻: 219.

Example 2: Synthesis of 2-chloro-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one

Phosphorous oxychloride (4.60g, 30 mmol) was added to dimethylformamide(32 ml) and stirred 20 min at 0°C. 2-Mercapto-3-methyl-6-pyrimidin-4-yl-pyrimidin-4-one (4.40 g, 20 mmol) was added to the solution and stirred 5 min and then stirred at 70°C for 1 hour. The reaction mixture was poured into ice water, neutralized by solid K₂CO₃, and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na₂SO₄ and evaporated *in vacuo*. Purification of the residue by silica gel column chromatography (ethyl acetate) gave the title compound (1.20 g, 27%).

¹H-NMR (CDCl₃) δ : 3.74(s, 3H), 7.56(s, 1H), 8.18 (d, J=5.1, 1H), 8.92 (d, J=5.1Hz, 1H),

9.30(s, 1H).

MS[M+H]⁺: 223.

Example 3: Synthesis of (S)-2-[2-(4-Methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one (Compound No. B079 in Table-1)

A solution of (S)-2-(4-methoxyphenyl)morpholine hydrochloride (0.30 g, 1.35 mmol), 2-chloro-3-methyl-6-(4-pyrimidyl)-pyrimidin-4-one (0.40 g, 1.75 mmol) and triethylamine (0.56 ml, 4.05 mmol) in tetrahydrofuran(6 ml) was refluxed for several hours. The reaction mixture was removed in vacuo. The residue was dissolved in 1N hydrochloric acid and extracted with dichloromethane. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel with ethyl acetate as the eluent to give the title compound (463 mg, 90%)

¹H-NMR (CDCl₃) δ : 3.12(dd, J=10.5, 12.9Hz, 1H), 3.31(dd, J=3.3, 12.3Hz, 1H), 3.51-3.63(m, 2H), 3.58(s, 3H), 3.83(s, 3H), 3.90-4.30(m, 2H), 4.67(dd, J=2.1, 10.5Hz, 1H), 6.91-6.96(m, 2H), 7.32-7.36(m, 3H), 8.14(dd, J=1.2, 5.1Hz, 1H), 8.86(d, J=5.1Hz, 1H), 9.27(d, J=1.2Hz, 1H).

MS[M+H]⁺: 380.

Example 4: Synthesis of (S)-2-[2-(4-fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one (Compound No. B031 in Table-1)

A solution of (S)-2-(4-fluorophenyl)morpholine hydrochloride (108.6 mg, 0.60 mmol), 2-chloro-3-methyl-6-pyrimidyl-4-pyrimidin-4-one (88.4 mg, 0.40 mmol) and triethylamine (0.27 ml, 2.0 mmol) in tetrahydrofuran(2 ml) was stirred at room temperature for several hours. The precipitate was filtered off after cooling and solvent was removed in vacuo. The residue was washed with ethyl acetate to give

the title compound (100 mg, 74%).

¹H-NMR (CDCl₃) δ : 3.09(dd, J=12.9, 10.8Hz, 1H), 3.29(m, 1H), 3.52-3.64(m, 2H), 3.59(s, 3H), 4.00(m, 1H), 4.21(m, 1H), 4.72(dd, J=10.5, 2.1Hz, 1H), 7.07-7.13(m, 2H), 7.38-7.43(m, 3H), 8.13 (dd, J=5.4, 1.2Hz, 1H), 8.88 (d, J=5.1Hz, 1H), 9.28(s, 1H).
MS[M⁺H]⁺: 367.

Example 5: Synthesis of 2-[4-(4-Chlorobenzoyl)piperidin-1-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one (Compound No. D034 in Table-1)

A solution of (4-Chlorobenzoyl)piperidine hydrochloride (140 mg, 0.539 mmol), 2-chloro-3-methyl-6-(4-pyrimidyl)-pyrimidine-4-one (120 mg, 0.539 mmol) and triethylamine (0.188 ml, 1.35 mmol) in N,N-dimethylformamide(2 ml) was stirred at room temperature. After stirring for several hours, water was added to the reaction mixture. The precipitate was filtered, washed with water and dried to give the title compound (204 mg, 92%).

The compounds in the following table were prepared in the same manner as the methods described above. The compound numbers in the following table correspond to those shown in the above-described table of preferred compounds.

Table 2

Compound No.	¹ H-NMR (Solvent) δ :	[M+H] ⁺
A119	(CDCl ₃): 3.60(s, 3H), 5.03(d, J=3.9Hz, 2H), 6.14(brs, 1H), 7.14(s, 1H), 7.59(t, J=7.8Hz, 2H), 7.69(m, 2H), 8.08(m, 2H), 8.15(m, 1H), 8.86(d, J=5.1Hz, 1H), 9.28(s, 1H).	322
A121	(CDCl ₃): 3.60(s, 3H), 5.01(d, J=3.9Hz, 2H), 6.06(brs, 1H), 7.14(s, 1H), 7.40-7.89(m, 4H), 8.13(m, 1H), 8.87(d, J=5.1Hz, 1H), 9.28(s, 1H).	340
A124	(CDCl ₃): 3.61(s, 3H), 5.02(d, J=4.2Hz, 2H), 6.04(brs, 1H), 7.15(s, 1H), 7.51-8.15(m, 5H), 8.89(d, J=5.1Hz, 1H), 9.29(s, 1H).	356
A130	(CDCl ₃): 2.49(s, 3H), 3.61(s, 3H), 5.01(d, J=3.9Hz, 2H), 6.14(brs, 1H), 7.14(s, 1H), 7.44-8.18(m, 1H), 8.88(d, J=5.1Hz, 1H), 9.28(s, 1H).	336
B030	(CDCl ₃): 3.09(dd, J=12.9, 10.8Hz, 1H), 3.29(m, 1H), 3.52-3.64(m, 2H), 3.59(s, 3H), 4.00(m, 1H), 4.20(m, 1H), 4.72(dd, J=10.5, 2.1Hz, 1H), 7.07-7.13(m, 2H), 7.38-7.43(m, 3H), 8.13 (dd, J=5.1, 1.2Hz, 1H), 8.87 (d, J=5.1Hz, 1H), 9.28(s, 1H).	368
B032	(CDCl ₃): 3.09(1H, m), 3.29(1H, m), 3.52-3.64(5H, m), 4.00(1H, m), 4.21(1H, m), 4.72(1H, m), 7.07-7.13(2H, m), 7.38-7.43(3H, m), 8.13 (1H, d, J=5.4Hz), 8.87 (d, J=4.2Hz, 1H), 9.28(s, 1H).	368
B037	(CDCl ₃): 3.01(dd, J=12.9, 10.5Hz, 1H), 3.39(m, 1H), 3.52(m, 1H), 3.60(s, 3H), 3.80-4.22(m, 3H), 5.13(d, J=8.7Hz, 1H), 7.07-7.36(m, 4H), 7.58(m, 1H), 8.20(d, J=2.1Hz, 1H), 8.88 (d, J=5.1Hz, 1H), 9.28(s, 1H).	367
B082	(CDCl ₃): 3.12(dd, J=10.5, 13.2Hz, 1H), 3.20-3.40(m, 1H), 3.50-3.70(m, 2H), 3.59(s, 3H), 3.85(s, 3H), 3.90-4.30(m, 2H), 4.72(dd, J=2.1, 10.5Hz, 1H), 6.80-7.00(m, 2H), 7.30-7.40(m, 2H), 8.15(dd, J=1.2, 5.1Hz, 1H), 8.87(d, J=5.1Hz, 1H), 9.28(d, J=1.2Hz, 1H).	379
B084	(CDCl ₃): 2.82(1H,dd,J=10.3,12.7Hz),3.34(1H,dt,J=3.1,12.3Hz),3.56(1H,d,J=12.8Hz),3.64(3H,s),3.81(1H,d,J=12.2Hz),3.87(3H,s),4.01(1H,dt,J=2.4,11.8Hz),4.23(1H,dd,J=2.4,11.7Hz),5.08(1H,dd,J=1.5,10.1Hz),6.91(1H,d,J=8.3Hz),7.03(1H,t,J=7.5Hz),7.2-7.3(1H,m),7.34(1H,s),7.54(1H,d,J=7.5Hz),8.20(1H,d,J=4.9Hz),8.86(1H,d,J=5.1Hz),9.27(1H,s)	380
B085	(CDCl ₃): 2.82(1H,dd,J=10.2,12.9Hz),3.2-3.4(1H,m),(3.5-3.6(1H,m),3.63(3H,s),3.8-3.9(1H,m),3.87(3H,s),4.0-4.2(1H,m),4.2-4.3(1H,m),5.08(1H,dd,J=2.1,10.2Hz),6.91(1H,d,J=8.4Hz),7.03(1H,t,J=7.8Hz),7.2-7.3(1H,m),7.34(1H,s),7.54(1H,dd,J=1.5,7.8Hz),8.20(1H,dd,J=1.2,5.1Hz),8.86(1H,d,J=5.1Hz),9.27(1H,d,J=1.2Hz)	380

B102	(DMSO-d ₆): 3.2-3.3(1H, m), 3.42(3H, s), 3.5-3.6(1H, m), 3.6-3.7(1H, m), 3.7-3.8(1H, m), 3.79(6H, s), 3.9-4.0(2H, m), 5.3-5.4(1H, m), 6.91(1H, m), 6.69(2H, d, J=8.4Hz), 6.98(1H, s), 7.29(1H, t, J=8.4Hz), 8.21(1H, d, J=5.1Hz), 9.00(1H, d, J=5.1Hz), 9.29(1H, s).	410
B103	(CDCl ₃): 3.4-3.6(6H, m), 3.86(6H, s), 3.9-4.1(2H, m), 4.1-4.2(1H, m), 5.4-5.5(1H, m), 6.61(2H, d, J=8.4Hz), 7.2-7.4(2H, m), 8.2-8.3(1H, m), 8.86(1H, d, J=5.1Hz), 9.28(1H, d, J=0.9Hz)	410
B104	(CDCl ₃): 3.4-3.6(6H, m), 3.86(6H, s), 3.9-4.1(2H, m), 4.1-4.2(1H, m), 5.4-5.5(1H, m), 6.61(2H, d, J=8.4Hz), 7.2-7.4(2H, m), 8.2-8.3(1H, m), 8.86(1H, d, J=5.1Hz), 9.28(1H, d, J=0.9Hz)	410
B105	(CDCl ₃): 3.43-3.54(3H, m), 3.60(3H, s), 3.82(1H, dd, J=12.9, 11.1Hz), 3.98(1H, m), 4.22(1H, m), 5.55(1H, dd, J=11.1, 2.7Hz), 7.18-7.42(4H, m), 8.19(1H, dd, J=5.1, 1.2Hz), 8.87(1H, d, J=5.1Hz), 9.27(1H, s).	418
B106	(CDCl ₃): 3.43-3.54(3H, m), 3.60(3H, s), 3.82(1H, dd, J=12.9, 11.1Hz), 3.98(1H, m), 4.22(1H, m), 5.55(1H, dd, J=11.1, 2.7Hz), 7.18-7.42(4H, m), 8.20(1H, dd, J=5.1, 1.2Hz), 8.87(1H, d, J=5.1Hz), 9.28(1H, s).	418
B107	(CDCl ₃): 3.43-3.54(3H, m), 3.60(3H, s), 3.82(1H, dd, J=12.9, 11.1Hz), 3.98(1H, m), 4.22(1H, m), 5.55(1H, dd, J=11.1, 2.7Hz), 7.18-7.42(4H, m), 8.19(1H, dd, J=5.1, 1.2Hz), 8.87(1H, d, J=5.1Hz), 9.28(1H, s).	418
B112	(DMSO-d ₆): 1.87-2.02(m, 4H), 2.99-3.34(m, 7H), 3.49(s, 3H), 3.69-4.11(m, 3H), 4.33(d, J=5.7, 1H), 4.79(d, J=9.3Hz, 1H), 7.01(s, 1H), 7.52-7.65(m, 4H), 8.21 (d, J=4.8Hz, 1H), 9.00(d, J=5.1Hz, 1H), 9.30(s, 1H).	432
B126	(CDCl ₃): 0.3-0.4(2H, m), 0.6-0.7(2H, m), 1.2-1.3(1H, m), 2.79(1H, dd, J=10.3, 12.7Hz), 3.3-3.5(1H, m), 2.6-2.7(1H, m), 3.66(3H, s), 3.7-4.0(3H, m), 4.0-4.2(1H, m), 4.2-4.3(1H, m), 5.09(1H, dd, J=2.0, 10.1Hz), 6.85(1H, d, J=8.2Hz), 6.9-7.1(1H, m), 7.2-7.3(1H, m), 7.33(1H, s), 7.53(1H, dd, J=1.6, 7.6Hz), 8.18(1H, dd, J=1.3, 5.1Hz), 8.87(1H, d, J=5.2Hz), 9.27(1H, d, J=1.4Hz)	420
B140	(CDCl ₃): 2.0-2.1(4H, m), 3.16(1H, dd, J=10.7, 12.8Hz), 3.2-3.4(5H, m), 3.5-3.6(2H, m), 3.57(3H, s), 3.9-4.1(1H, m), 4.1-4.2(1H, m), 4.61(1H, dd, J=2.2, 10.7Hz), 6.58(2H, d, J=8.5Hz), 7.27(1H, d, J=8.5Hz), 7.34(1H, s), 8.15(1H, dd, J=1.2, 5.1Hz), 8.86(1H, d, J=5.1Hz), 9.27(1H, d, J=1.2Hz)	419
B217	(CDCl ₃): 1.19(s, 3H), 1.21(s, 3H), 2.89-3.00(m, 2H), 3.38(m, 1H), 3.60(s, 3H), 3.61(m, 1H), 3.82(s, 3H), 5.00(m, 1H), 6.94(d, J = 8.5Hz, 2H), 7.34(s, 1H), 7.37(d, J = 8.5Hz, 2H), 8.14(dd, J = 5.4, 1.4Hz, 1H), 8.87 (d, J = 5.4Hz, 1H), 9.27 (d, J = 1.4Hz, 1H).	408
B225	(CDCl ₃): 3.3-3.6(3H, m), 3.64(3H, s), 4.0-4.4(3H, m), 5.22(1H, dd, J=2.7, 9.9Hz), 7.38(1H, s), 7.4-7.6(2H, m), 7.95(1H, d, J=7.7Hz), 8.03(1H, d, J=8.0Hz), 8.17(1H, d, J=1.0, 5.0Hz), 8.87(1H, d, J=5.0Hz), 9.28(1H, d, J=1.0Hz)	407

B237	(CDCl ₃): 2.99(1H, dd, J=12.9, 10.5Hz), 3.22-3.53(4H, m), 3.60(3H, s), 3.83-4.18(3H, m), 4.58-4.66(2H, m), 4.97(1H, dd, J=10.2, 2.1Hz), 6.91(1H, m), 7.17-7.31(2H, m), 7.34(1H, s), 8.26(1H, dd, J=5.1, 1.2Hz), 8.87(1H, d, J=4.8Hz), 9.28(1H, s).	392
B238	(CDCl ₃): 2.80(1H, dd, J=12.5, 10.2Hz), 3.32(1H, m), 3.55(1H, m), 3.63(3H, s), 3.75(1H, m), 3.85(3H, s), 4.01(1H, m), 4.21(1H, m), 5.00(1H, d, J=10.2Hz), 6.61-6.75(2H, m), 7.34(1H, s), 7.48(1H, m), 8.19(1H, dd, J=5.2, 1.1Hz), 8.87(d, J=5.1Hz, 1H), 9.28(s, 1H).	398
B239	(CDCl ₃): 3.4-3.7(4H, m), 3.59(3H, s), 3.9-4.0(1H, m), 4.18(1H, dd, J=1.6, 12.1Hz), 5.38(1H, dd, J=4.1, 9.3Hz), 7.0-7.1(1H, m), 7.2-7.3(2H, m), 7.36(1H, s), 8.20(1H, dd, J=1.2, 5.2Hz), 8.87(1H, d, J=5.2Hz), 9.28(1H, d, J=1.2Hz)	402
B240	(CDCl ₃): 2.81(1H, dd, J=10.4, 12.8Hz), 3.2-3.4(1H, m), 3.63(3H, s), 3.7-3.8(1H, m), 4.0-4.1(1H, m), 4.2-4.3(1H, m), 5.07(1H, dd, J=2.0, 10.3Hz), 7.0-7.2(2H, m), 7.35(1H, s), 7.63(1H, dd, J=6.2, 8.7Hz), 8.16(1H, dd, J=1.4, 5.2Hz), 8.86(1H, d, J=5.2Hz), 9.27(1H, d, J=1.4Hz)	402
B241	(CDCl ₃): 1.33(3H, d, J=6.0Hz), 1.38(3H, d, J=6.0Hz), 2.72(1H, dd, J=12.9, 10.5Hz), 3.35(1H, m), 3.55-3.71(5H, m), 4.03-4.21(2H, m), 4.57(1H, m), 4.96(1H, dd, J=9.9, 1.8Hz), 6.58-6.71(2H, m), 7.34(1H, s), 7.46(1H, dd, J=8.7, 7.5Hz), 8.17(1H, dd, J=5.1, 1.2Hz), 8.87(1H, d, J=5.4Hz), 9.28(1H, s).	426
B242	(CDCl ₃): 3.3-3.4(1H, m), 3.5-3.6(2H, m), 3.60(3H, s), 3.83(3H, s), 3.9-4.0(1H, m), 4.0-4.1(1H, m), 4.1-4.2(1H, m), 4.96(1H, dd, J=2.4, 10.2Hz), 6.50(1H, s), 7.0-7.1(1H, m), 7.2-7.3(2H, m), 7.38(1H, s), 8.15(1H, dd, J=1.2, 4.8Hz), 8.89(1H, d, J=5.4Hz), 9.29(1H, d, J=1.2Hz)	421
B243	(CDCl ₃): 2.99(1H, dd, J=12.9, 10.5Hz), 3.22-3.53(4H, m), 3.61(3H, s), 3.83-4.18(3H, m), 4.58-4.66(2H, m), 4.97(1H, dd, J=10.2, 2.1Hz), 6.92(1H, m), 7.17-7.31(2H, m), 7.35(1H, s), 8.26(1H, d, J=5.4Hz), 8.87(1H, d, J=5.1Hz), 9.28(1H, s).	392
B244	(DMSO-d ₆): 3.2-3.4(1H, m), 3.42(3H, s), 3.80(6H, s), 3.5-4.0(5H, m), 5.26(1H, d, J=8.2Hz), 6.58(1H, s), 6.62(1H, s), 6.98(1H, s), 8.21(1H, dd, J=1.2, 5.0Hz), 9.01(1H, d, J=5.1Hz), 9.30(1H, d, J=1.2Hz)	428
B245	(DMSO-d ₆): 3.2-3.4(1H, m), 3.42(3H, s), 3.80(6H, s), 3.5-4.0(5H, m), 5.26(1H, d, J=8.2Hz), 6.58(1H, s), 6.62(1H, s), 6.98(1H, s), 8.21(1H, dd, J=1.2, 5.0Hz), 9.01(1H, d, J=5.1Hz), 9.30(1H, d, J=1.2Hz)	428
B246	(DMSO-d ₆): 2.17(3H, s), 2.27(3H, s), 2.7-2.9(1H, m), 3.1-3.3(1H, m), 3.48(3H, s), 3.6-3.7(1H, m), 3.7-4.0(5H, m), 4.0-4.1(1H, m), 4.9-5.0(1H, m), 6.85(1H, s), 7.00(1H, s), 7.19(1H, s), 8.24(1H, d, J=5.0Hz), 9.01(1H, d, J=4.9Hz), 9.30(1H, s)	408
B247	(DMSO-d ₆): 0.29-0.31(2H, m), 0.50-0.54(2H, m), 1.18(1H, m), 2.78(1H, m), 3.34(1H, m), 3.52(3H, s), 3.71-4.16(6H, m), 4.92(1H, m), 6.80(1H, m), 6.92(1H, m), 7.01(1H, s), 7.43(1H, m), 8.23(1H, d, J=4.8Hz), 9.00(1H, d, J=2.1Hz), 9.30(1H, s).	438

B248	(DMSO-d ₆) : 2.85(1H, dd, J=10.4, 12.9 Hz), 3.2-3.3(1H, m), 3.49(3H, s), 3.6-3.7(1H, m), 3.8-4.0(2H, m), 3.94(3H, s), 4.1-4.2(1H, m), 5.04(1H, d, J=8.9 Hz), 7.02(1H, s), 7.27(1H, d, J=8.6 Hz), 7.79(1H, s), 7.85(1H, dd, J=2.0, 8.5 Hz), 8.25(1H, d, J=5.2 Hz), 9.02(1H, d, J=5.2 Hz), 9.30(1H, s)	405
B249	(DMSO-d ₆) : 2.79(1H, dd, J=10.2, 12.9 Hz), 3.1-3.3(1H, m), 3.48(3H, s), 3.6-3.7(1H, m), 3.8-4.0(2H, m), 3.87(3H, s), 4.0-4.1(1H, m), 4.9-5.0(1H, m), 7.01(1H, s), 7.07(1H, dd, J=1.8, 8.1 Hz), 7.14(1H, d, J=2.1 Hz), 7.44(1H, d, J=8.1 Hz), 8.24(1H, d, J=5.4 Hz), 9.01(1H, d, J=5.1 Hz), 9.30(1H, s)	414
B250	(DMSO-d ₆) : 3.2-3.6(2H, m), 3.48(3H, s), 3.6-3.7(2H, m), 3.7-4.1(2H, m), 3.87(3H, s), 5.1-5.3(1H, m), 6.7-7.0(2H, m), 7.00(1H, s), 8.2-8.3(1H, m), 9.0-9.1(1H, m), 9.31(1H, s)	416
B251	(CDCl ₃) : 3.3-3.5(1H, m), 3.62(3H, s), 3.5-3.7(2H, m), 4.0-4.4(3H, m), 5.36(1H, dd, J=2.7, 9.9 Hz), 7.3-7.4(2H, m), 7.6-7.7(2H, m), 7.9-8.0(1H, m), 8.15(1H, dd, J=1.4, 5.3 Hz), 8.87(1H, d, J=5.3 Hz), 9.28(1H, d, J=1.2 Hz).	391
B252	(CDCl ₃) : 3.3-3.5(1H, m), 3.62(3H, s), 3.5-3.7(2H, m), 3.9-4.3(3H, m), 5.36(1H, dd, J=2.6, 9.8 Hz), 7.3-7.4(2H, m), 7.5-7.7(2H, m), 7.97(1H, d, J=8.3 Hz), 8.1-8.2(1H, m), 8.87(1H, d, J=5.2 Hz), 9.28(1H, s).	391
B253	(DMSO-d ₆) : 2.7-2.9(1H, m), 3.2-3.3(1H, m), 3.49(3H, s), 3.6-3.7(1H, m), 3.9-4.0(5H, m), 4.1-4.2(1H, m), 5.0-5.1(1H, m), 7.02(1H, s), 7.49(1H, d, J=6.8 Hz), 7.55(1H, s), 7.62(1H, d, J=7.9 Hz), 8.24(1H, d, J=4.0 Hz), 9.01(1H, d, J=5.1 Hz), 9.29(1H, s)	405
B254	(CDCl ₃) : 3.3-3.5(4H, m), 3.57(3H, s), 3.67(1H, t, J=11.1 Hz), 3.87(3H, s), 3.95(1H, t, J=11.7 Hz), 4.1-4.2(1H, m), 5.24(1H, d, J=9.3 Hz), 6.4-6.6(2H, m), 7.34(1H, s), 8.19(1H, dd, J=1.2, 5.1 Hz), 8.87(1H, m), 8.87(1H, d, J=5.1 Hz), 9.28(1H, d, J=1.2 Hz)	416
B255	(DMSO) : 2.92(1H, dd, J=10.1, 12.9 Hz), 3.22-3.28(1H, m), 3.50(3H, s), 3.66-3.71(1H, d, J=12.7 Hz), 3.82-3.96(2H, m), 3.90(3H, s), 4.13(1H, d, J=12.5 Hz), 5.08(1H, d, J=9.0 Hz), 7.01(1H, s), 7.15(1H, d, J=8.7 Hz), 7.24-7.30(2H, m), 7.58-7.69(4H, m), 8.25(1H, d, J=4.9 Hz), 9.01(1H, d, J=5.0 Hz), 9.30(1H, s)	474
B256	(DMSO) : 2.95(1H, dd, J=10.3, 12.8 Hz), 3.21-3.34(1H, m), 3.50(3H, s), 3.68(1H, d, J=13.1 Hz), 3.87-3.96(2H, m), 3.91(3H, s), 4.13(1H, d, J=11.2 Hz), 5.10(1H, d, J=8.1 Hz), 7.02(1H, s), 7.20(1H, d, J=8.6 Hz), 7.40-7.50(1H, m), 7.64-7.71(1H, m), 7.76(1H, d, J=2.3 Hz), 7.98-8.06(1H, m), 8.26(1H, dd, J=1.1, 5.0 Hz), 8.53-8.54(1H, m), 8.85(1H, d, J=2.4 Hz), 9.01(1H, d, J=5.1 Hz), 9.29(1H, d, J=1.3 Hz)	457
B257	(DMSO-d ₆) : 2.83(1H, m), 3.26(1H, m), 3.50(3H, s), 3.68(1H, m), 3.84-4.11(3H, m), 5.00(1H, m), 6.62-6.66(2H, m), 7.04(1H, s), 7.38(1H, m), 8.33(1H, d, J=5.1 Hz), 8.99(1H, d, J=3.9 Hz), 9.28(1H, s), 10.21(1H, s).	384

B258	(DMSO-d ₆) :2.8-2.9(1H,m),3.2-3.3(1H,m),3.50(3H,s),3.69(1H,dd,J=11.7Hz),3.8-4.0(5H,m),4.1-4.2(1H,m),5.06(1H,d,J=8.7Hz),7.02(1H,s),7.2-7.6(6H,m),7.72(2H,d,J=7.8Hz),8.26(1H,d,J=4.8Hz),9.01(1H,d,J=5.1Hz),9.03(1H,s)	456
B259	(CDCl ₃) :1.9-2.1(4H,m),2.83(1H,dd,J=9.9,12.6Hz),3.2-3.4(5H,m),3.5-3.6(1H,m),3.63(3H,s),3.79(3H,s),3.8-3.9(1H,m),4.0-4.1(1H,m),4.2-4.3(1H,m),5.05(1H,dd,J=2.1,9.9Hz),6.50(1H,dd,J=3.0,9.0Hz),6.8-6.9(2H,m),7.33(1H,s),8.21(1H,dd,J=1.2,5.1Hz),8.86(1H,d,J=5.1Hz),9.27(1H,d,J=1.2Hz)	449
B260	(CDCl ₃) :2.0-2.1(4H,m),2.89(1H,dd,J=10.2,12.9Hz),3.3-3.4(5H,m),3.4-3.6(1H,m),3.61(3H,s),3.7-3.8(1H,m),3.75(3H,s),4.0-4.1(1H,m),4.2-4.3(1H,m),4.99(1H,dd,J=2.1,10.2Hz),6.08(1H,d,J=2.1Hz),6.21(1H,dd,J=2.1,8.4Hz),7.3-7.4(2H,m),8.20(1H,dd,J=1.5,5.1Hz),8.86(1H,d,J=5.1Hz),9.27(1H,d,J=1.2Hz)	449
B261	(DMSO) :2.87(1H, dd J=10.5, 12.9 Hz), 3.20-3.29(1H, m), 3.50(3H,s), 3.68(1H, d, J=12.6 Hz), 3.85-3.98(2H, m), 3.91(3H, s), 4.12(1H, d, J=9.9 Hz), 5.08(1H, d, J=9.3 Hz), 7.02(1H, s), 7.18(1H, d, J=8.7 Hz), 7.29-7.33(2H, m), 7.36-7.40(1H, m), 7.48-7.54(2H, m), 7.64(1H, s), 8.26(1H, d, J=5.1 Hz), 9.01(1H, d, J=5.1 Hz), 9.30(1H, s)	474
B262	(DMSO) :2.92(1H, dd, J=10.5, 12.3 Hz), 3.23-3.31(1H, m), 3.50(3H, s), 3.79(1H, d, J=12.9 Hz), 3.82(3H, s), 3.87-3.95(2H, m), 3.90(3H, s), 4.13(1H, d, J=10.8 Hz), 5.08(1H, d, J=10.8 Hz), 6.91(1H, dd, J=1.5, 8.1 Hz), 7.01(1H, s), 7.12-7.19(3H, m), 7.34-7.39(1H, m), 7.63(1H, dd, J=1.5, 7.5 Hz), 7.71(1H, s), 8.26(1H, d, J=5.1 Hz), 9.01(1H, d, J=5.1 Hz), 9.30(1H, s)	486
B263	(DMSO) :2.86(1H, dd, J=10.8, 12.3 Hz), 3.20-3.27(1H, m), 3.50(3H, s), 3.67(1H, d, J=12.9 Hz), 3.87-3.95(2H, m), 3.91(3H, s), 4.10(1H, d, J=10.5 Hz), 5.08(1H, d, J=9.3 Hz), 7.02(1H, s), 7.17(1H, d, J=8.7 Hz), 7.40-7.45(2H, m), 7.49-7.55(2H, m), 7.73(1H, s), 8.26(1H, d, J=5.4 Hz), 9.02(1H, d, J=5.1 Hz), 9.31(1H, s)	524
B264	(DMSO) :1.65-1.74(4H, m), 2.38-2.46(4H, m), 2.78(1H, dd, J=10.2, 12.9 Hz), 3.19-3.29(1H, m), 3.49(3H, s), 3.52(2H, d, J=4.0 Hz), 3.67(1H, d, J=13.2 Hz), 3.80-3.91(2H, m), 3.83(3H, s), 4.11(1H, d, J=13.8 Hz), 5.01(1H, d, J=8.5 Hz), 6.98(1H, d, J=8.4 Hz), 7.00(1H, s), 7.22(1H, dd, J=2.1, 8.4 Hz), 7.40(1H, d, J=1.9 Hz), 8.25(1H, dd, J=1.3, 5.2 Hz), 9.01(1H, d, J=5.1 Hz), 9.30(1H, d, J=1.1 Hz)	463
B265	(DMSO) :3.01(1H, dd, J=11.4, 12.3 HZ), 3.15-3.22(1H, m), 3.47(3H, s), 3.70-3.78(2H, m), 3.89-3.96(1H, m), 4.08(1H, d, J=11.4 Hz), 4.76(1H, d, J=9.6 Hz), 7.01(1H, s), 7.38-7.44(1H, m), 7.52-7.55(1H, m), 7.79-7.81(1H, m), 8.22(1H, d, J=4.8 Hz), 8.99(1H, d, J=5.1 Hz), 9.30(1H, s)	446

B266	(DMSO) :2.94(1H, dd, J=10.4, 12.8 Hz), 3.23-3.31(1H, m), 3.49(3H, s), 3.69(1H, d, J=13.2 Hz), 3.85-3.95(2H, m), 3.90(3H, s), 4.13(1H, d, J=10.0 Hz), 5.08(1H, d, J=8.9 Hz), 7.01(1H, s), 7.13-7.17(2H, m), 7.47-7.50(3H, m), 7.67(1H, dd, J=2.2, 8.5 Hz), 7.75(1H, d, J=2.3 Hz), 8.25(1H, d, J=5.0 Hz), 9.01(1H, d, J=5.3 Hz), 9.30(1H, s)	474
B267	(DMSO) :2.85(1H, dd, J=10.4, 12.8 Hz), 3.19-3.26(1H, m), 3.50(3H, s), 3.67(1H, d, J=13.2 Hz), 3.76(3H, s), 3.87-3.94(2H, m), 3.88(3H, s), 4.10(1H, d, J=9.8 Hz), 5.06(1H, d, J=9.7 Hz), 6.99-7.04(2H, m), 7.07-7.11(2H, m), 7.24-7.37(2H, m), 7.42-7.46(1H, m), 7.54(1H, s), 8.26(1H, d, J=5.2 Hz), 9.01(1H, d, J=5.0 Hz), 9.30(1H, s)	486
B268	(DMSO) :2.91(1H, dd, J=10.4, 12.8 Hz), 3.20-3.31(1H, m), 3.50(3H, s), 3.69(1H, d, J=12.8 Hz), 3.79(3H, s), 3.86-3.95(2H, m), 3.88(3H, s), 4.13(1H, d, J=10.1 Hz), 5.07(1H, d, J=8.8 Hz), 7.00-7.02(3H, m), 7.12(1H, d, J=8.6 Hz), 7.53-7.57(3H, m), 7.66(1H, d, J=2.2 Hz), 8.26(1H, d, J=5.2 Hz), 9.01(1H, d, J=6.0 Hz), 9.30(1H, s)	486
B269	(DMSO) :2.79(1H, dd, J=10.0, 12.7 Hz), 3.12-3.24(1H, m), 3.49(3H, s), 3.67(1H, d, J=12.3 Hz), 3.81(3H, s), 3.87-3.91(2H, m), 4.04-4.10(1H, m), 5.00(1H, d, J=8.4 Hz), 6.70-6.75(1H, m), 6.92-7.01(5H, m), 7.04-7.08(1H, m), 7.15-7.20(2H, m), 7.24(1H, d, J=2.6 Hz), 7.94(1H, s), 8.26(1H, d, J=4.6 Hz), 9.01(1H, d, J=5.2 Hz), 9.30(1H, s)	471
B270	(CDCl ₃): 2.71(1H, dd, J=12.5, 10.3Hz), 3.24(3H, s), 3.33(1H, m), 3.51(1H, m), 3.69(1H, m), 4.00(1H, m), 4.22(1H, m), 5.04(1H, m), 5.06(2H, s), 6.68-6.78(2H, m), 7.30(1H, s), 7.36-7.40(5H, m), 7.51(1H, m), 8.15(1H, m), 8.81(1H, d, J=5.1Hz), 9.26(1H, s).	474
B271	(CDCl ₃): 3.37-3.53(3H, m), 3.60(3H, s), 3.86(1H, m), 4.05(1H, m), 4.18(1H, m), 5.00(1H, m), 6.78(1H, s), 7.25-7.38(3H, m), 7.50-7.61(2H, m), 8.17(1H, dd, J=5.1, 1.2Hz), 8.88(1H, d, J=5.1Hz), 9.29(1H, s).	390
B272	(CDCl ₃): 3.36-3.53(3H, m), 3.60(3H, s), 3.86(1H, m), 4.05(1H, m), 4.18(1H, m), 5.00(1H, dd, J=10.2, 2.4Hz), 6.78(1H, s), 7.25-7.38(3H, m), 7.50-7.61(2H, m), 8.17(1H, dd, J=5.1, 1.2Hz), 8.88(1H, d, J=5.1Hz), 9.29(1H, s).	390
B273	(CDCl ₃): 3.36-3.54(3H, m), 3.59(3H, s), 3.87(1H, m), 4.03(1H, m), 4.04(3H, s), 4.18(1H, m), 5.01(1H, m), 6.77(1H, s), 6.83(1H, m), 7.17-7.19(2H, m), 7.38(1H, s), 8.17(1H, d, J=4.2Hz), 8.87(1H, d, J=5.1Hz), 9.28(1H, s).	420

B274	(DMSO-d ₆): 1.8-2.2(4H,m), 2.9-3.2(3H,m), 3.2-3.5(3H,m), 3.50(3H,s), 3.70(1H,d,J=12.9Hz), 3.91(3H,s), 3.8-4.3(3H,m), 4.41(2H,d,J=4.2Hz), 5.10(1H,d,J=9.9Hz), 7.02(1H,s), 7.18(1H,d,J=8.4Hz), 7.4-7.6(2H,m), 7.6-7.8(2H,m), 7.80(1H,s), 7.96(1H,s), 8.27(1H,d,J=4.5Hz), 9.03(1H,d,J=4.8Hz), 9.31(1H,s), 11.2(1H,brd)	539
B275	(CDCl ₃): 1.9-2.1(4H,m), 3.17(1H,dd,J=10.613.0Hz), 3.2-3.4(5H,m), 3.5-3.6(1H,m), 3.58(3H,s), 3.6-3.7(1H,m), 3.9-4.1(1H,m), 4.2-4.3(1H,m), 4.6-4.7(1H,m), 6.5-6.6(1H,m), 6.60(1H,s), 6.68(1H,d,J=7.6Hz), 7.2-7.3(1H,m), 7.34(1H,s), 8.16(1H,d,J=5.7Hz), 8.85(1H,d,J=5.1Hz), 9.28(1H,d,J=1.3Hz)	419
B276	(CDCl ₃): 1.9-2.1(4H,m), 3.17(1H,dd,J=10.613.0Hz), 3.2-3.4(5H,m), 3.5-3.6(1H,m), 3.58(3H,s), 3.6-3.7(1H,m), 3.9-4.1(1H,m), 4.2-4.3(1H,m), 4.6-4.7(1H,m), 6.5-6.6(1H,m), 6.60(1H,s), 6.68(1H,d,J=7.6Hz), 7.2-7.3(1H,m), 7.34(1H,s), 8.16(1H,d,J=5.7Hz), 8.85(1H,d,J=5.1Hz), 9.28(1H,d,J=1.3Hz)	419
B277	(CDCl ₃): 2.88(1H, m), 3.37(1H, m), 3.58(1H, m), 3.65(3H, s), 3.86(1H, m), 3.91(3H, s), 4.03(1H, m), 4.24(1H, m), 5.12(1H, m), 7.09(1H, s), 7.13-7.48(6H, m), 7.60(1H, d, J=4.8Hz), 8.22(1H, d, J=5.1Hz), 8.87(1H, d, J=5.1Hz), 9.28(1H, s).	474
B278	(CDCl ₃): 2.86(1H, dd, J=12.6, 10.5Hz), 3.36(1H, m), 3.56(1H, m), 3.65(3H, s), 3.84(1H, m), 3.94(3H, s), 4.03(1H, m), 4.24(1H, m), 5.11(1H, m), 7.03-7.07(2H, m), 7.19-7.45(5H, m), 7.60(1H, d, J=4.8Hz), 8.21(1H, d, J=4.2Hz), 8.67(1H, d, J=5.1Hz), 9.28(1H, s).	474
B279	(CDCl ₃): 2.86(1H, dd, J=12.3, 9.9Hz), 3.36(1H, m), 3.58(1H, m), 3.60(3H, s), 3.84(1H, m), 3.93(3H, s), 4.03(1H, m), 4.24(1H, m), 5.11(1H, m), 7.03(1H, s), 7.04-7.41(3H, m), 7.35(1H, s), 7.52-7.60(3H, m), 8.21(1H, dd, J=5.4, 1.5Hz), 8.67(1H, d, J=5.1Hz), 9.28(1H, d, J=1.5Hz).	474
B280	(DMSO): 2.88(1H, dd, J=10.5, 12.6 Hz), 3.24-3.32(1H, m), 3.51(3H, s), 3.70(1H, d, J=12.9 Hz), 3.89-3.97(2H, m), 3.92(3H, s), 4.15(1H, d, J=11.4 Hz), 5.09(1H, d, J=9.0 Hz), 7.01(1H, s), 7.17(1H, d, J=8.4 Hz), 7.28-7.32(1H, m), 7.80-7.92(2H, m), 8.04(1H, d, J=8.7 Hz), 8.25-8.27(2H, m), 8.64(1H, d, J=4.2 Hz), 9.01(1H, d, J=5.4 Hz), 9.30(1H, s)	457
B281	(DMSO): 2.91(1H, dd, J=10.3, 12.9 Hz), 3.20-3.30(1H, m), 3.50(3H,s), 3.69(1H, d, J=13.0 Hz), 3.88-3.97(2H, m), 3.91(3H, s), 3.95(3H, s), 4.15(1H, d, J=9.9 Hz), 5.08(1H, d, J=8.6 Hz), 6.73(1H, d, J=8.2 Hz), 7.01(1H, s), 7.17(1H, d, J=8.7 Hz), 7.48(1H, d, J=7.5 Hz), 7.73-7.78(1H, m), 8.06-8.09(1H, m), 8.15(1H, d, J=2.1 Hz), 8.25(1H, dd, J=1.1, 5.1 Hz), 9.00(1H, d, J=5.2 Hz), 9.30 (1H, d, J=0.9 Hz)	487

B282	(DMSO) :2.93(1H, dd, J=10.5, 12.9 Hz), 3.22-3.30(1H, m), 3.50(3H, s), 3.69(1H, d, J=13.2 Hz), 3.86-3.95(2H, m), 3.89(6H, s), 4.13(1H, d, J=9.6 Hz), 5.08(1H, d, J=8.4 Hz), 6.90(1H, d, J=8.7 Hz), 7.01(1H, s), 7.16(1H, d, J=8.7 Hz), 7.58-7.63(1H, m), 7.68(1H, d, J=2.4 Hz), 7.96(1H, dd, J=2.7, 8.4 Hz), 8.26(1H, dd, J=1.2, 4.8 Hz), 8.42(1H, d, J=2.7 Hz), 9.01(1H, d, J=5.4 Hz), 9.30(1H, d, J=1.5 Hz)	517
B283	(DMSO) :2.87(1H, dd, J=10.3, 12.8 Hz), 3.20-3.28(1H, m), 3.50(3H, s), 3.67(1H, d, J=12.2 Hz), 3.87-3.94(2H, m), 3.89(3H, s), 3.94(6H, s), 4.11(1H, d, J=10.2 Hz), 5.06(1H, d, J=9.0 Hz), 7.01(1H, s), 7.13(1H, d, J=8.6 Hz), 7.46(1H, dd, J=2.2, 8.6 Hz), 7.57(1H, d, J=2.1 Hz), 8.25(1H, d, J=5.2 Hz), 8.32(1H, s), 9.01(1H, d, J=5.2 Hz), 9.30 (1H, s)	518
B284	(CDCl ₃) :2.3-2.4(1H,m),2.5-2.6(1H,m),3.2-3.4(1H,m),3.4-3.7(3H,m),3.59(3H,s),3.9-4.0(1H,m),4.1-4.2(2H,m),4.3-4.4(1H,m),6.88(1H,dd,J=1.2,8.4Hz),7.01(1H,t,J=7.5Hz),7.26(1H,t,J=8.4Hz),7.36(1H,s),7.63(1H,dd,J=1.5,7.5Hz),8.13(1H,dd,J=1.2,5.1Hz),8.86(1H,d,J=5.1Hz),9.28(1H,d,J=1.2Hz)	392
B285	(CDCl ₃) :1.8-2.0(3H,m),2.4-2.5(1H,m),3.2-3.4(1H,m),3.46(3H,s),3.4-3.6(1H,m),3.7-3.8(1H,m),3.70(1H,d,J=13.2 Hz),3.88(1H,d,J=13.2Hz),4.1-4.2(1H,m),4.2-4.4(2H,m),7.02(1H,dd,J=1.5,7.8Hz),7.1-7.2(1H,m),7.2-7.3(1H,m),7.32(1H,s),7.6-7.7(1H,m),8.15(1H,dd,1.5,5.4Hz),8.87(1H,d,J=5.4Hz),9.27(1H,d,J=1.5Hz)	406
C401	(DMSO-d ₆) :1.5-1.7(1H,m),1.8-2.0(2H,m),2.0-2.1(1H,m),2.9-3.1(1H,m),3.1-3.2(1H,m),3.43(3H,s),3.6-3.8(1H,m),3.8-4.0(2H,m),6.96(1H,s),7.55(2H,t,J=5.6Hz),7.67(1H,t,J=7.8Hz),8.03(2H,d,J=7.8Hz),8.18(1H,d,J=5.4Hz),8.99(1H,d,J=4.8Hz),9.30(1H,s)	376
C501	(CDCl ₃) :3.3-3.6(3H,m),3.58(3H,s),3.88(1H,d,J=13.3Hz),3.9-4.1(1H,m),4.1-4.3(1H,m),5.08(1H,dd,J=2.6,9.4Hz),7.35(1H,s),7.50(1H,t,J=7.8Hz),7.63(1H,t,J=7.4Hz),8.06(1H,d,J=7.3Hz),8.13(1H,dd,J=0.9,5.0Hz),8.87(1H,d,J=5.2Hz),9.28(1H,d,J=0.8Hz)	378
C789	(CDCl ₃) :3.3-3.6(3H,m),3.58(3H,s),3.88(1H,d,J=13.3Hz),3.9-4.1(1H,m),4.1-4.3(1H,m),5.08(1H,dd,J=2.6,9.4Hz),7.35(1H,s),7.50(1H,t,J=7.8Hz),7.63(1H,t,J=7.4Hz),8.06(1H,d,J=7.3Hz),8.13(1H,dd,J=0.9,5.0Hz),8.87(1H,d,J=5.2Hz),9.28(1H,d,J=0.8Hz)	378
C790	(CDCl ₃) :3.3-3.6(3H,m),3.58(3H,s),3.88(1H,d,J=13.3Hz),3.9-4.1(1H,m),4.1-4.3(1H,m),5.08(1H,dd,J=2.6,9.4Hz),7.35(1H,s),7.50(1H,t,J=7.8Hz),7.63(1H,t,J=7.4Hz),8.06(1H,d,J=7.3Hz),8.13(1H,dd,J=0.9,5.0Hz),8.87(1H,d,J=5.2Hz),9.28(1H,d,J=0.8Hz)	378
D034	(CDCl ₃): 1.95-2.06(m, 4H), 3.13(m, 2H), 3.49(m, 1H), 3.55(s, 3H), 3.73(m, 2H), 7.33(s, 1H), 7.49(d, J=8.7Hz, 2H), 7.92(d, J=8.7Hz, 2H), 8.17(d, J=5.0Hz, 1H), 8.87(d, J=5.0Hz, 1H), 9.28(s, 1H).	410

Test Example: Inhibitory activity of the medicament of the present invention against P-GS1 phosphorylation by bovine cerebral TPK1

A mixture containing 100 mM MES-sodium hydroxide (pH 6.5), 1 mM magnesium acetate, 0.5 mM EGTA, 5 mM β -mercaptoethanol, 0.02% Tween 20, 10% glycerol, 12 μ g/ml P-GS1, 41.7 μ M [γ -³²P] ATP (68 kBq/ml), bovine cerebral TPK1 and a compound shown in Table (a final mixture contained 1.7% DMSO deriving from a solution of a test compound prepared in the presence of 10% DMSO) was used as a reaction system. The phosphorylation was started by adding ATP, and the reaction was conducted at 25°C for 2 hours, and then stopped by adding 21% perchloric acid on ice cooling. The reaction mixture was centrifuged at 12,000 rpm for 5 minutes and adsorbed on P81 paper (Whatmann), and then the paper was washed four times with 75 mM phosphoric acid, three times with water and once with acetone. The paper was dried, and the residual radioactivity was measured using a liquid scintillation counter. The results are shown in the table below. The test compound markedly inhibited the P-GS1 phosphorylation by TPK1. The results strongly suggest that the medicaments of the present invention inhibit the TPK1 activity, thereby suppress the A β neurotoxicity and the PHF formation, and that the medicaments of the present invention are effective for preventive and/or therapeutic treatment of Alzheimer disease and the above-mentioned diseases.

Table 3

Compound No.	IC ₅₀ (nM)
A119	24
A121	19
A124	11
A130	30
B030	11
B031	5
B032	32
B037	3
B079	2.9
B082	4.6
B084	1.2
B085	0.87
B102	0.441
B103	0.23
B104	4.5
B105	0.27
B106	1.2
B107	40
B112	2.1
B126	23
B140	3.7
B217	26.1
B225	12
B237	0.821
B238	0.47
B239	0.74
B240	3.5
B241	4.6
B242	6.9
B243	4.2
B244	0.17
B245	1.3
B246	1.1
B247	15
B248	0.78
B249	0.83
B250	0.56
B251	2.4
B252	1
B253	0.7
B254	0.24
B255	4.6
B256	0.64
B257	7.4
B258	1.4
B259	1.2
B260	0.77
B261	1.4

B262	1.3
B263	13
B264	0.6
B265	0.6
B266	1.6
B267	1.2
B268	1.7
B269	1.1
B270	27
B271	4.2
B272	7.1
B273	4.3
B274	0.57
B275	7
B276	4.8
B277	1.4
B278	1.1
B279	1.2
B280	0.60
B281	0.84
B282	1.0
B283	1.9
B284	11
B285	26
C401	1.1
C501	0.56
C789	38
C790	0.64
D034	1.1

Formulation Example

(1) Tablets

The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 1	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft capsules

The ingredients below were mixed by an ordinary method and filled in soft capsules.

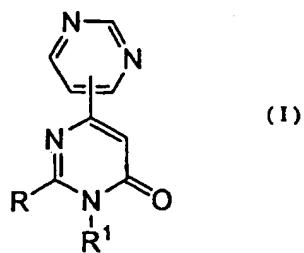
Compound of Example 1	30 mg
Olive oil	300 mg
Lecithin	20 mg

Industrial Applicability

The compounds of the present invention have TPK1 inhibitory activity and are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases caused by abnormal advance of TPK1 such as neurodegenerative diseases (e.g. Alzheimer disease) and the above-mentioned diseases.

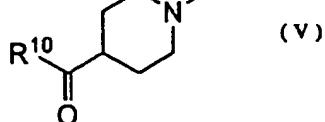
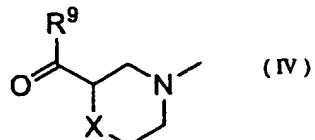
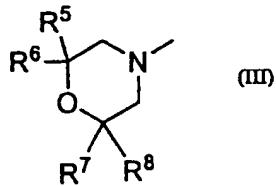
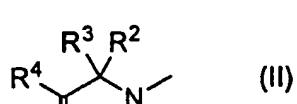
CLAIMS

1. A pyrimidone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:



wherein R¹ represents a C₁-C₁₂ alkyl group which may be substituted;

R represents any one of groups represented by the following formulas (II) to (V):



wherein R² and R³ independently represent a hydrogen atom or a C₁-C₈ alkyl group;

R⁴ represents a benzene ring which may be substituted, a naphthalene ring which may be substituted, an indan ring which may be substituted, a tetrahydronaphthalene ring which may be substituted, or an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of

oxygen atom, sulfur atom and nitrogen atom, and having 5 to 10 ring-constituting atoms in total;

R⁵ represents a C₁-C₈ alkyl group which may be substituted, a C₃-C₈ cycloalkyl group which may be substituted, a benzene ring which may be substituted, a naphthalene ring which may be substituted, an indan ring which may be substituted, a tetrahydronaphthalene ring which may be substituted, or an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms in total;

R⁶ represents a hydrogen atom, a C₁-C₈ alkyl group which may be substituted, a benzene ring which may be substituted;

or R⁵ and R⁶ may bind to each other to form together with the carbon to which R⁵ and R⁶ are attached an optionally substituted spiro carbocyclic ring having 3 to 11 ring-constituting atoms in total;

R⁷ and R⁸ independently represent a hydrogen atom or a C₁-C₈ alkyl group, or R⁷ and R⁸ may combine to each other to form a C₂-C₆ alkylene group;

R⁹ and R¹⁰ represent a C₁-C₈ alkyl group which may be substituted, a C₃-C₈ cycloalkyl group which may be substituted, a benzene ring which may be substituted, a naphthalene ring which may be substituted, an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms in total, or R⁹ and R¹⁰ represent -N(R¹¹)(R¹²) wherein R¹¹ represents a hydrogen atom, a C₁-C₈ alkyl group; and R¹² represents a C₁-C₈ alkyl group, a benzene ring which may be substituted, a naphthalene ring which may be substituted, or an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms in total;

and X represents CH_2 , O or NR^{13} wherein R^{13} represents a hydrogen atom or a $\text{C}_1\text{-C}_8$ alkyl group.

2. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 1, wherein R^1 is methyl group.

3. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 1 or 2, wherein R is the group represented by formula (II).

4. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 3, wherein each of R^2 and R^3 is hydrogen atom.

5. A pyrimidone derivative which is selected from the group consisting of:
3-methyl-2-(2-oxo-2-phenylethylamino)-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
3-methyl-2-(2-oxo-2-(3-fluorophenyl)ethylamino)-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
3-methyl-2-(2-oxo-2-(4-fluorophenyl)ethylamino)-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
3-methyl-2-(2-oxo-2-(3-chlorophenyl)ethylamino)-6-pyrimidin-4-yl-3H-pyrimidin-4-one and
3-methyl-2-(2-oxo-2-(3-methylphenyl)ethylamino)-6-pyrimidin-4-yl-3H-pyrimidin-4-one

or a salt thereof, or a solvate thereof or a hydrate thereof.

6. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 1 or 2, wherein R is the group represented by formula (III).

7. The pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof according to claim 6, wherein R^6 is hydrogen atom.

8. The pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof according to claim 7, wherein each of R^7 and R^8 is hydrogen atom.

9. The pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof according to claim 7, wherein each of R^7 and R^8 is methyl group.

10. A pyrimidone derivative which is selected from the group consisting of:

2-[2-(4-Fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; (S)-2-[2-(4-Fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2-Fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; (S)-2-[2-(2-Fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(4-Chlorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; 2-[2-(3-Chlorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; 2-[2-(2-Chlorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; (S)-2-[2-(2-Chlorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(4-Bromophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; (S)-2-[2-(4-Bromophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(3-Bromophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; (S)-2-[2-(3-Bromophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2-Bromophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; 2-[2-(4-Methylphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; 2-[2-(3-Methylphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; 2-[2-(2-Methylphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; (S)-2-[2-(2-Methylphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(4-Cyanophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; 2-[2-(3-Cyanophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; (S)-2-[2-(3-Cyanophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one.

one;

2-[2-(2-Cyanophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(4-Methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(4-Methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(3-Methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(3-Methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one

2-[2-(2-Methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2-Methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2-Ethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
2-[2-(2-Trifluoromethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(5-Fluoro-2-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(4-Fluoro-2-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(4-Fluoro-2-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2,5-Dimethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2,5-Dimethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2-Chloro-4,5-difluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2-Chloro-4,5-difluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2-Bromo-4-fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2,4-Difluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2,4-Difluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2,6-Dimethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2,6-Dimethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2,4-Dimethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2,4-Dimethoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2,6-Dichlorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2,6-Dichlorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2,6-Difluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2,6-Difluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2-Chloro-6-fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidi

n-4-one;

(S)-2-[2-(2-Chloro-6-fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(4-Fluoro-3-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(5-Cyano-2-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(5-Cyano-2-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(4-Cyano-2-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(4-Cyano-2-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2,4-Difluoro-6-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2,4-Difluoro-6-methoxyphenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(4-(Pyrrolidin-1-yl-methyl)phenyl)morpholino-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(4-(Pyrrolidin-1-yl-methyl)phenyl)morpholino-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(1-Naphthyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2-Naphthyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2-Naphthyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

2-[2-(2,3-dihydrobenzofuran-7-yl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

(S)-2-[2-(2,3-dihydrobenzofuran-7-yl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

pyrimidin-4-one;

2-[2-(Benzofuran-2-yl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
and

(S)-2-[2-(Benzofuran-2-yl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one

or a salt thereof, or a solvate thereof or a hydrate thereof.

11. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 1 or 2, wherein R is the group represented by formula (IV).

12. The pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof according to claim 11, wherein R⁹ is a benzene ring which may be substituted.

13. The pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof according to claim 11, wherein X is CH₂.

14. The pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof according to claim 11, wherein X is O.

15. A pyrimidone derivative which is selected from the group consisting of:
2-[3-(4-Fluorobenzoyl)piperidin-1-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
2-(3-Benzoylpiperidin-1-yl)-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
2-[3-(2-Methoxybenzoyl)piperidin-1-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
2-[3-(4-Methoxybenzoyl)piperidin-1-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
2-[2-(4-Fluorobenzoyl)morpholine-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
2-(2-Benzoylmorpholine-4-yl)-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;
2-[2-(2-Methoxybenzoyl)morpholine-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; and
2-[2-(4-Methoxybenzoyl)morpholine-4-yl]-3-methyl-6-pyrimidin-4-yl-3H-

pyrimidin-4-one;

or a salt thereof, or a solvate thereof or a hydrate thereof.

16. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 1 or 2, wherein R is the group represented by formula (V).

17. The pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof according to claim 16, wherein R¹⁰ is a benzene ring which may be substituted.

18. The pyrimidone derivative or the salts thereof, or the solvate thereof or the hydrate thereof according to claim 16, wherein R¹⁰ is a heterocyclic ring having 1 to 4 hetero atoms selected oxygen atom, sulfur atom and nitrogen atom, and having total ring-constituting atoms of 5 to 10 which may be substituted.

19. A pyrimidone derivative which is selected from the group consisting of: 2-[4-(4-Chlorobenzoyl)piperidin-1-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; or a salt thereof, or a solvate thereof or a hydrate thereof.

20. A medicament comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivative represented by formula (I) and a salt thereof, and a solvate thereof and a hydrate thereof according to claim 1.

21. A tau protein kinase 1 inhibitor selected from the group consisting of the pyrimidone derivative represented by formula (I) and a salt thereof, and a solvate thereof and a hydrate thereof according to claim 1.

22. The medicament according to claim 20 which is used for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity.

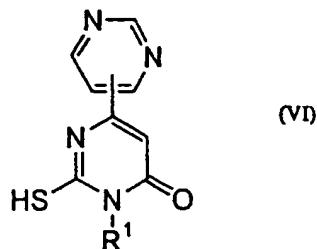
23. The medicament according to claim 20 which is used for preventive and/or therapeutic treatment of a neurodegenerative disease.

24. The medicament according to claim 23, wherein the disease is selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents,

Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration, frontotemporal dementia, vascular dementia, traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma.

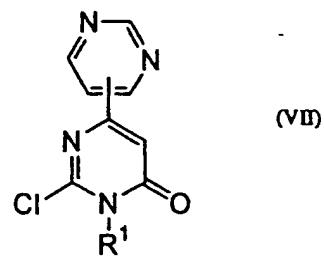
25. The medicament according to claim 20, wherein the disease is selected from the group consisting of non-insulin dependent diabetes, obesity, manic depressive illness, schizophrenia, alopecia, breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia, and a virus-induced tumor.

26. A pyrimidone derivative represented by formula (VI) or a salt thereof, or a solvate thereof or a hydrate thereof:



wherein R¹ represents a C₁-C₁₂ alkyl group which may be substituted.

27. A pyrimidone derivative represented by formula (VII) or a salt thereof, or a solvate thereof or a hydrate thereof:



wherein R¹ represents a C₁-C₁₂ alkyl group which may be substituted.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 02/09684

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/46 C07D239/56 C07D239/34 C07D413/14 C07D401/14
A61K31/505 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 18758 A (MITSUBISHI CHEMICAL) 6 April 2000 (2000-04-06) page 0; claims	1,20-25

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

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- *E* earlier document but published on or after the International filing date
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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the International search

12 November 2002

Date of mailing of the International search report

21/11/2002

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 02/09684

Patent document cited in search report	Publication date		Patent family member(s)		Publication date
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		CA	2345065 A1		06-04-2000
		CN	1328552 T		26-12-2001
		EP	1115721 A1		18-07-2001
		WO	0018758 A1		06-04-2000
		JP	2002525366 T		13-08-2002